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PITUITARY GONADOTROPIC EXTRACTS FOR TREATMENT OF AMENORRHEA, MENORRHAGIA, AND STERILITY*

RALPH E. CAMPBELL, M.D., AND ELMER L. SEVRINGHAUS, M.D.,
MADISON, WIS.

(From the Departments of Obstetrics and Gynecology, and Medicine, University of Wisconsin)

IN A number of the disorders of menstrual rhythm and of fertility, endocrine deficiencies are assumed to be major factors. Numerous reports have appeared in the past decade to illustrate the types of tissue reactions found in the uterus, vagina, and ovaries with experimentally produced endocrine disturbances in animals. Attempts to build diagnostic differentiations on this foundation have made progress, as we have indicated in a previous paper.[1] It is increasingly our impression that the endocrine responsibility for amenorrhea, oligomenorrhea, menorrhagia, irregular cycles, and sterility with anovulatory bleeding is to be considered pituitary hypofunction. The various clinical pictures mentioned are due to variations in quantity of gonadotropic hormones liberated and to abnormalities in the timing of this secretion which determines the cyclic activity of the ovaries. One way to prove such a thesis would be by quantitative assay of blood from patients, as compared with normally fertile and regular women. This method has been attempted by competent investigators, but suffers from such difficulties as a lack of information about normal cycles, debate as to the significance of certain

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It was the pleasure and good fortune of the authors to have the participation of Dr. F. L. Hisaw in the earlier years of the studies here reported. We gladly record our gratitude for the assistance of Drs. Wm. E. Bayley and J. Stewart in tissue study, of Mrs. June Golden in vaginal epithelial study, and Miss Linda Arneson, whose dependable preparation of tissues has contributed to our confidence in the comparison of biopsy specimens.

types of assay technique, and the expense of extended assays of specimens throughout one or more cycles. Endometrial biopsies at selected times in the cycle help to avoid some of these problems. They fall short of giving quantitative measures of the amount of ovarian hormones acting, and therefore of the amount of gonadotropic hormones available. The use of the vaginal smear study of Papanicolaou and Shorr[2] has enabled us to proceed further in the direction of time and intensity analysis of the disturbances mentioned above. The manner in which these methods are combined will be illustrated by case studies. We present at this time cases selected to show several types in which success or failure has attended the therapy prescribed after diagnostic studies had been made. The therapeutic results contribute further evidence to validate the diagnostic grouping. The cases presented have been under observation long enough to warrant certain deductions even though they are no more striking than other cases studied for shorter periods of time, but with similar results. Treatment may not achieve desired results because of many reasons ranging from inaccurate diagnosis through inadequate cooperation to inability to simulate even roughly the natural rate of secretion of gonadotropic materials by the intact anterior pituitary gland.

The therapy has been based on the hypodermic administration of aqueous extracts of the anterior lobe of standardized potency. Our most extensive experience is with the use of the extract as originally prepared by our former colleagues, Hisaw and Fevold,[3] marketed by Chappel Bros. Laboratory under the name of "Prephysin." More recently we have used "gonadotropic antuitrin," a Parke-Davis preparation made from hog pituitary and supplied to us through the courtesy of Dr. E. A. Sharpe. Still more recently we have used "Gonadogen," a pregnant mare's serum preparation, furnished us by Dr. G. Cartland of the Upjohn Laboratory. We are greatly indebted to the three laboratories for the generous supplies of these materials for this clinical study. The potency of the extracts has been checked for us at times by Drs. F. L. Hisaw and R. K. Meyer in the Department of Zoology. The only difficulties attending the use of the extracts has been a variable local reaction at the site of injection in many cases. Rarely has this interrupted the plan of treatment. In two cases urticarial reactions demonstrated allergic sensitization which necessitated discontinuance of injection. No allergic reactions have occurred *after* the first series of injections, a fact which surprised us since the extracts are known to contain small amounts of protein. The doses employed have been 1.0 c.c. daily or on alternate days, as indicated in the charts. These doses contained from 5 to 100 "units" each, although the definition of the unit is only roughly similar for the three preparations referred to above.

The timing of the therapy is considered of especial importance. As our concepts of the time of increasing activity in the pituitary, the ovaries, and the endometrium have developed, we have been convinced that the sharp increase in the secretory action of the follicle occurs at about the onset of a menstrual flow. We have therefore adopted the

onset of flow as the optimal time at which to begin use of a gonadotropic factor when follicle stimulation was the objective. Since there is increasing certainty that in a fertile twenty-eight-day cycle ovulation occurs on about the fourteenth day, we have attempted to concentrate the therapy in the first fourteen days. The reason for our insistence on not using continuous injections of a potent gonadotropic substance is that such treatment has produced follicle cysts in animals and may conceivably do so in the human being. It is our belief that long continued (and possibly low intensity) pituitary stimulation is the background of many cases of polycystic ovaries. With this caution in mind we have been alert to the possibility of producing cysts by our program, but to date have been unable to detect such a result. Judging from results with monkeys it should be possible to induce ovulation in a matured follicle by the intravenous injection of a mixture of the two anterior pituitary hormones.[4] We have made numerous attempts to do this but our success has not been dependable enough to present. This we attribute to the difficulty in securing a regular supply of extract which is high in its content of the "luteinizing hormone." Therefore we have confined our attempts to the use of mixed follicle stimulating and luteinizing materials hypodermically, in interrupted series beginning with the onset of each flow. When there have been long periods of amenorrhea, we have resumed therapy usually after thirty-two days from the last preceding flow or the last preceding series of injections. This plan was devised to coordinate the injected pituitary materials with those secreted by the patient's gland during the same cycle. It is possible that ultimately we may come to an even more physiologic plan of treatment with continuous daily therapy, varying the doses when we have better evidence bearing on the rate of activity of the normal gland. At present we prefer to remain on the side of undertreating the patient, even though we may have failures when larger doses might have produced greater success.

SECONDARY AMENORRHEA

E. M., unmarried, 23-year-old white woman, was referred because of obesity, variable edema, and amenorrhea. Menarche occurred at 13 years of age, cycles were of four-weeks' type with one week of flow, but infrequent menses and obesity appeared and amenorrhea of two years preceded the study. Symptoms included irritability, hot flashes, palpitation, dyspnea, vertigo, morbid melancholy and worrying, and paresthesias. Basal metabolic rate +20 per cent and blood pressure 130/80. Pelvic examination showed a definitely small uterus but no other findings. Endometrial biopsy procured tissue without evidence of any activity, i.e., essentially as in a castrate (Fig. 1, *a*). The only therapy used was the 1,200 calorie reduction diet and "prephysin" given in series of 7 to 10 daily doses of 25 units each, at 4-week intervals. Two "menstrual" flows occurred, but a second biopsy taken four weeks after the fourth series of injections was begun showed no more active tissues than before therapy. The treatment was increased to 15 doses in each series, and after 8 such series flows of five to seven days each began to occur at intervals between four and six weeks. Dietary cooperation was almost nil for the first year, but improved when the patient began to see results of the injections. After 21 series of injections, in twenty-two months, during which 13 flows had occurred, the patient was allowed to go through a cycle without therapy, and on the twenty-fourth day another biopsy was obtained. This proved to have a follicular type of activity about as might be expected in the second week of a normal cycle, although not too well developed. The

result was considered indicative of progress. The details of injection were altered to accord with the routine advised above, i.e., each series was begun when and only when a flow appeared, instead of at arbitrary four-week intervals.

Regularity of menstrual rhythm continued its improvement toward a four-weeks' type. A fourth biopsy, taken late in the fourth week after 5 more cycles of treatment, showed no changes, however (Fig. 1, *b*). It was concluded that further therapy required still greater intensity of pituitary stimulation, plus probably intravenous

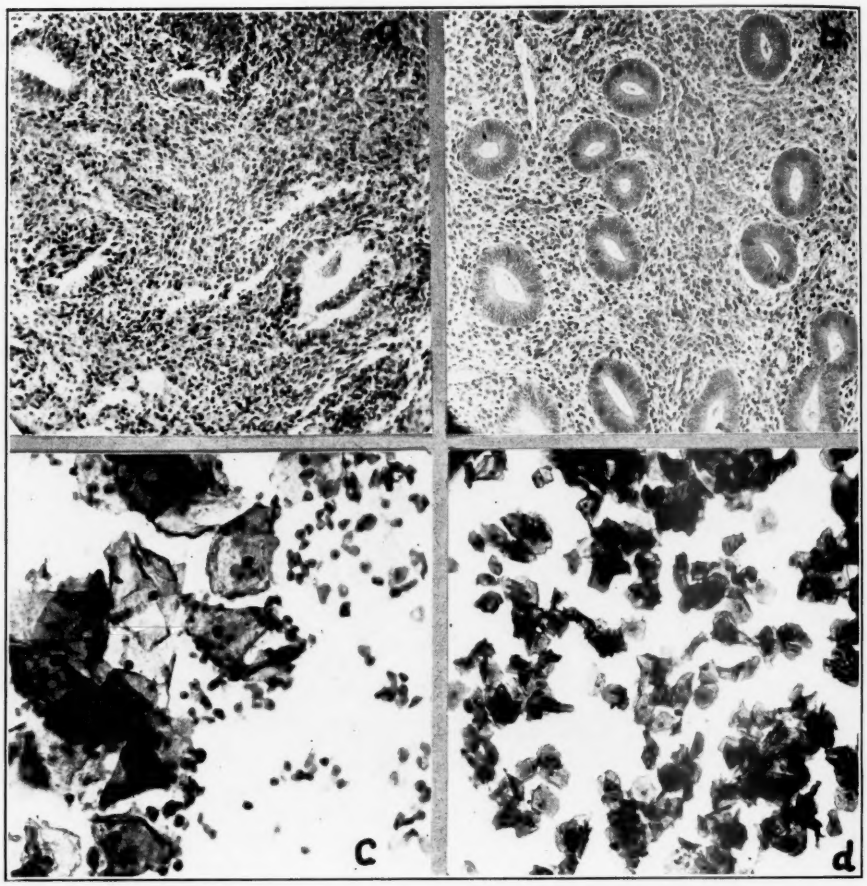

Fig. 1.—Case E. M. (*a*) First biopsy, showing "castrate" inactivity. (*b*) Fourth biopsy, on twenty-fifth day of cycle under treatment, showing only estrin activity. (*c*) Vaginal smear on ninth day of same cycle with (*b*), showing some cornified cells and many small cells from deep layers. (*d*) Vaginal smear on 16th day of a cycle when 15 daily doses of 100 units each of prephysin were given, showing increased clarity, with some cornified cells.

administration of the material to secure ovulation. The number of daily injections was increased to 15, and next the anterior pituitary material used was changed to doses with 100 units per c.c., 4 times the potency previously employed. As a method for studying the activity of the ovaries in response to this stimulation, vaginal epithelium was examined by the Papanicolaou and Shorr technique. Samples taken on the fourteenth to sixteenth days of several cycles showed obvious estrogenic hormone activity (Fig. 1, *c* and *d*), but this was below the intensity associated with the end of the normal second week.

The partial results accomplished in this woman, after thirty-four months during which the cycles of therapy have been interrupted only twice, demonstrate that large doses of gonadotropic material will probably be required for the treatment of even secondary amenorrhea. There has been clinical improvement, shown by menses occurring every four to six weeks for two years, with rare shorter intervals, by mammary development, by improved secondary sex characters, and by improved interest in weight control as a consequence of which she has followed diet limitations and reduced by 27 pounds during the interval. It is debatable whether the results justify the costs. The patient and referring physician continue to feel that they do.

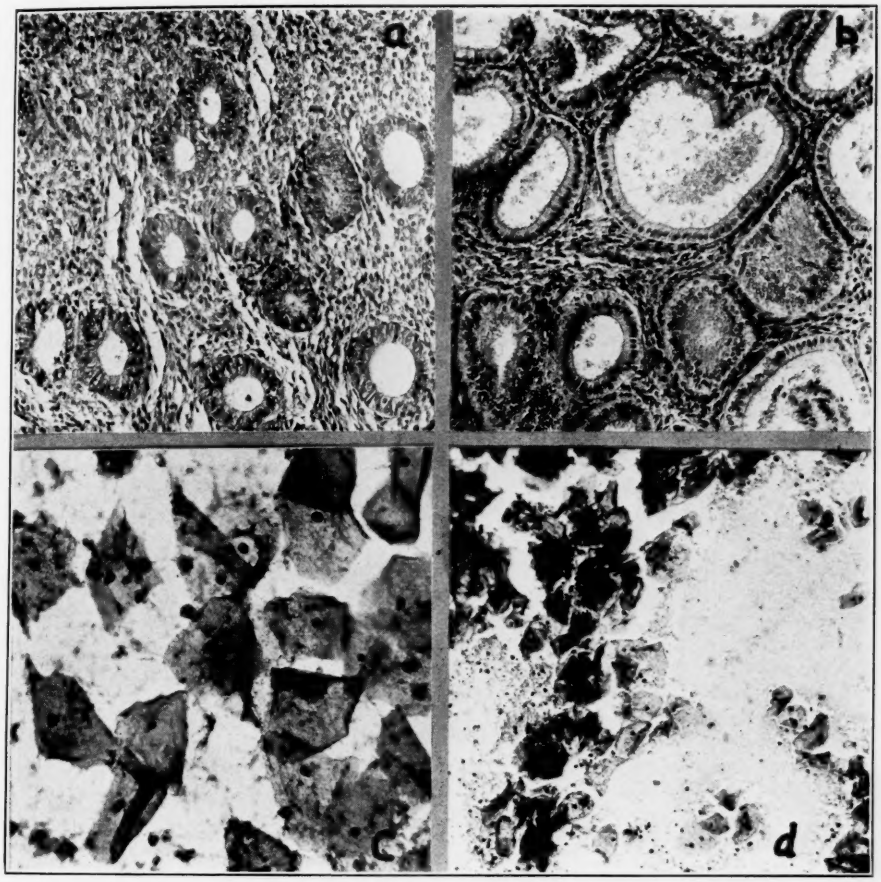

Fig. 2.—Case El. Mo. (*a*) Biopsy on twenty-seventh day of thirty-three-day cycle, showing low intensity of estrin action. (*b*) Biopsy on thirty-first day of thirty-four-day cycle showing some evidence of progestin action. (*c*) Vaginal smear on fourteenth day of a cycle without therapy, showing a few cornified cells, but not typically clear specimen of full estrin activity. (*d*) Vaginal smear of twenty-seventh day of same cycle (proved anovulatory), simulating premenstrual picture.

E. M., unmarried, twenty-two-year-old white woman, referred because of obesity, amenorrhea, and lack of secondary sex characters, had not flowed for thirteen months. Menarche occurred at sixteen years of age; the cycle was always irregular, infrequent, and with brief flows. There were no nervous symptoms. Basal metabolism had been brought up to normal range by use of thyroid and was continued so throughout the entire period of study, but without effect other than that, combined with the 1,200 calorie diet, weight was brought down to optimal levels. Pelvic examination showed nothing unusual. During the first year estrogenic material was used, but with no

subjective changes and no flow. Then for six months pregnancy urine concentrate was given without help. Then there followed seven months with combined pregnancy urine and "prephysin," during which interval 5 flows appeared. For the following year the patient took only thyroid, and recorded 9 flows in twelve months. Following this came a period of thirty months' use of "prephysin," in series of 5 doses of 25 units each, repeated 25 times, with obvious improvement in secondary characteristics (leading to engagement to be married), and the occurrence of four- to five-week cycles, with three- to six-day flows. The "prephysin" was then omitted for 8 cycles, following which there was a tendency to longer cycles, less copious flow, and the patient returned to the therapy with return of more normal type of flow. Biopsy was not obtained at the start of the study, but on two occasions during the treatment it was secured. The earlier of these (Fig. 2, *a*), in the late fourth week of a thirty-three-day cycle after 9 series of injections showed only low grade follicular action, but seven months later on the thirty-first day of a thirty-four-day cycle, a good progestational endometrium was demonstrated (Fig. 2, *b*). After 11 cycles of therapy in the course of twelve months, the pituitary injections were interrupted for a single month. On the fourteenth day of the cycle a vaginal epithelial sample showed moderate development of estrogenic stimulation. This subsided during the next two weeks as expected. Determination of pregnandiol excretion in twenty-four-hour urine samples during the fourth week showed that a corpus luteum did not form, i.e. there was no pregnandiol excretion. This confirms Papanicolaou and Shorr's report[2] that the "premenstrual" vaginal smear cannot be accepted as evidence of progestin action.

This patient has made definite gain under combined therapy. The use of thyroid cannot be considered the chief cause of the improvement, for it was used throughout. Ovarian activity is complete at times in that the estrogenic and progestational hormones are being formed, although the intensity and regularity are such that probably fertility is not yet possible. It is considered that further treatment with increased doses of pituitary material is justified and necessary if results are to be optimal.

Z. R., an unmarried woman of 24 years, had been under medical care for irregular and infrequent menses since age of 19. Menarche at 15 had been followed by flows at intervals of six weeks to three months, duration four to five days, without other unusual findings. There was a slight tendency to obesity. The lowest basal metabolic test recorded was 23 per cent below the expected level. Thyroid therapy was begun at the age of 19, and continued, with determinations of basal rate, to maintain the patient at the normal level. This led to no improvement in the menstrual rhythm. Pelvic examination at age of 24 showed a distinctly small uterus, with small ovaries. The breasts were rather small. An endometrial biopsy was obtained on the forty-first day after a flow appeared, and showed a very low intensity of estrogenic hormone stimulation. This was followed at once by a three-day flow. (Biopsy technique never produces this result in normal types of cycle.) The treatment with pituitary extract was begun, using 10 doses of 25 units each in fifteen days, repeated each four weeks. After 5 series of doses the progress was not evident, and the dose was changed to 100 units at each injection. Vaginal epithelium examined during the second week of such series of injections failed to show more than a trace of estrogenic hormone influence in spite of fifteen consecutive days' therapy. The material used was changed to gonadogen (Upjohn). After the use of 15 daily doses of 10 units each, and also of 15 daily doses of 20 units each, the estrogenic activity was no more intense than it had been previously.

As a consequence of this period of intensive stimulation, with varying doses of two types of gonadotropic material, but with little evidence of improvement in ovarian performance, this patient has been advised to abandon treatment. The prospect is of continued irregularity and sterility. The clinical impression is that the ovaries have for some unknown reason a very limited capacity to respond to stimulation by the pituitary. Aside from the details given there are no evidences of a lack of feminization, or other health problem.

The varying responsiveness to pituitary stimulation shown by these cases is typical of that seen in a large group of patients with complaints of infrequent menses and periods of amenorrhea. The use of the biopsy of endometrium and the vaginal epithelium readings obtained with a pipetted sample enable the clinician to determine in a relatively short period of time whether progress is being made. If estrogenic hormone effects do not become increasingly intense under pituitary stimulation in such patients it seems wise to increase the dosage, and if that fails, to abandon treatment.

MENORRHAGIA

Although the occurrence of excessively long menstrual flow seems diametrically opposite to the amenorrheic state, there is a growing appreciation of the similarity between menorrhagia and amenorrhea in the endocrine activity involved. Although not all cases of prolonged flow are due to absence of progestin action, there are more menorrhagic women with flow from a poorly developed estrin endometrium than with any other type. This statement obviously excludes cases with neoplasm, sepsis, or pregnancy as factors in the flowing. Although our study of deficiencies in prothrombin time show that a few cases of menorrhagia are quickly relieved by the administration of vitamin K, this is probably an infrequent cause of bleeding from the uterus. A few examples of successful treatment of irregular and prolonged bleeding will demonstrate how we have applied methods similar to those described above for amenorrhea.

E. D. was examined at age of 17 because of irregular menstrual cycles at intervals of three to six weeks, with flow varying from two to sixteen days. This condition had been noted since the menarche at 13. Other findings included marked acne, some hot flushes, sweating spells, dyspneic attacks, and paresthesias. Secondary sex characters were not well developed. The basal metabolism was within normal limits. The physical examination including pelvic examination under an anesthetic was not remarkable except for small breasts. Endometrium obtained during a prolonged period of flow showed essentially normal estrogenic stimulation of the tissue, from which bleeding continued (Fig. 3). Since it was evident that the flow was anovulatory, attempts were made to initiate corpus luteum formation by the intravenous injection of 25 unit doses of prephysin. This is known to contain both the follicle stimulating and luteinizing activity of the anterior pituitary. This treatment was given between the eleventh and fourteenth days of three cycles, with results which were encouraging. The systemic and immediate reactions to the introduction of the extract intravenously caused such marked chill and fever, with nausea, that it was considered unwise to persist. The patient was not available for endometrial biopsy to determine whether a corpus luteum was formed at the time of this therapy. It was therefore determined to use the prephysin hypodermically as before described. After this had been done for 17 cycles in the next sixteen months, without any recurrence of menorrhagia, a biopsy was obtained in the early part of the third week without treatment in that cycle. This showed progestational effects within the limits of normal for the time (Fig. 3). The next flow followed five days later. This early flow and the characteristic cycle of twenty-one to twenty-four days which had developed during the treatment led to the belief that the intensity of progestin action was subnormal. After 5 more cycles with similar treatment the patient preferred to omit therapy and see how well the gain could be maintained. There was no essential difference in the next 10 cycles, but during the fifth cycle without treatment, twenty-four-hour urine samples were examined for pregnandiol. The total excretion

during seven days was only 12.2 mg., far below the accepted normal level. It is considered that this woman now has an intensity of pituitary and ovarian activity which is below normal. Since menorrhagia is no longer occurring, and since secondary sex characters have developed satisfactorily, she prefers to omit treatment. In thirteen months without therapy she has had 17 flows, intervals three to five weeks, duration three to nine days, typically four to five days.

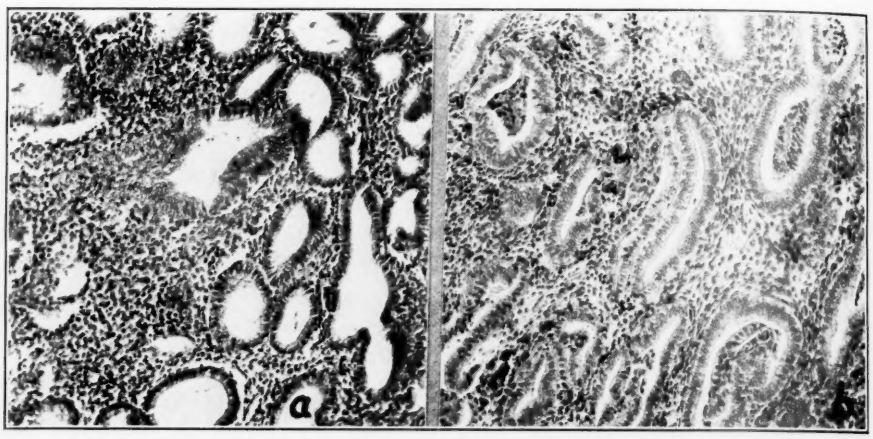

Fig. 3.—Case. E. D. (*a*) First biopsy, during third week of menorrhagia; irregular glands, with estrin action. (*b*) Biopsy on sixteenth day of twenty-one-day cycle, showing early effects of progestin.

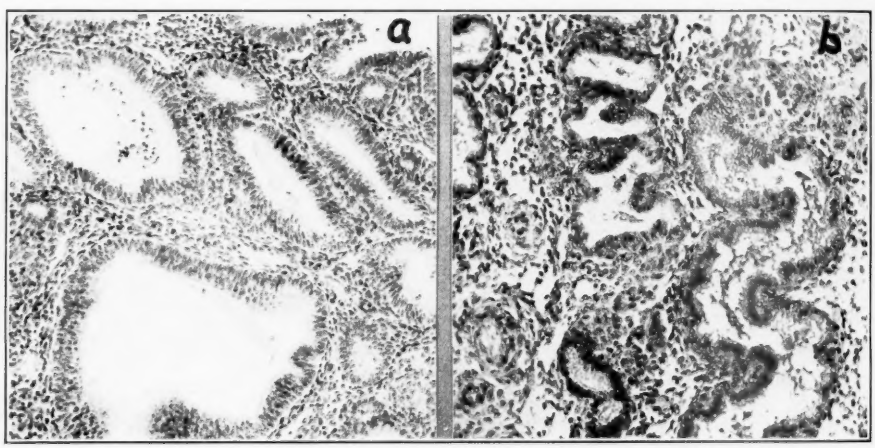

Fig. 4.—Case K. M. (*a*) Curette specimen during menorrhagia, showing the "Swiss cheese" picture, resulting from sustained estrin action. (*b*) Biopsy in fourth week, after therapy, showing evidences of progestin action.

K. M. was referred at the age of 29 because of menorrhagia during flows which lasted three to four days. Anemia was not significant. Menses had been occurring at intervals of three to four weeks. There were occasional flows of two weeks' duration. Mumps had occurred preceding these symptoms at age of 28, but without recognized oophoritis. Other complaints included acne, asthenia without hypotension, nervous irritability, palpitation, headaches, insomnia, morbid melancholy and worrying. The basal metabolism was repeatedly found to be 23 to 30 per cent above the normal, but the clinical picture was not typical of thyrotoxicosis. Pelvic examina-

tion revealed an enlarged and retroverted uterus, which was replaced and supported by a pessary. Curettage done during a prolonged flow removed tissue with areas of glandular and cystic hyperplasia, resembling the "Swiss cheese" type (Fig. 4, *a*). The menorrhagia recurred in the second cycle after the curettage, and therefore treatment was initiated with anterior pituitary extract. The product employed was gonadotropic antuitrin (Parke-Davis and Co.). This material contained 5 to 10 units per c.c.; doses of 1 c.c. were given in similar routines to that used for prephysin. Local reactions were very slight. Improvement was evident after a few months. In the fourth week of a cycle without treatment, endometrium obtained with a biopsy punch showed typical effects of progestin (Fig. 4, *b*), and the flow began on the following day. It was evident that the ovary was forming a corpus luteum. Treatment was resumed for 6 cycles, which varied from five to six weeks in length. Although the duration of flow was still sometimes long, it was not excessively heavy. The patient was feeling well, and preferred to try an observation period without therapy. This was successful, for the next 5 flows, at least, were of ordinary duration.

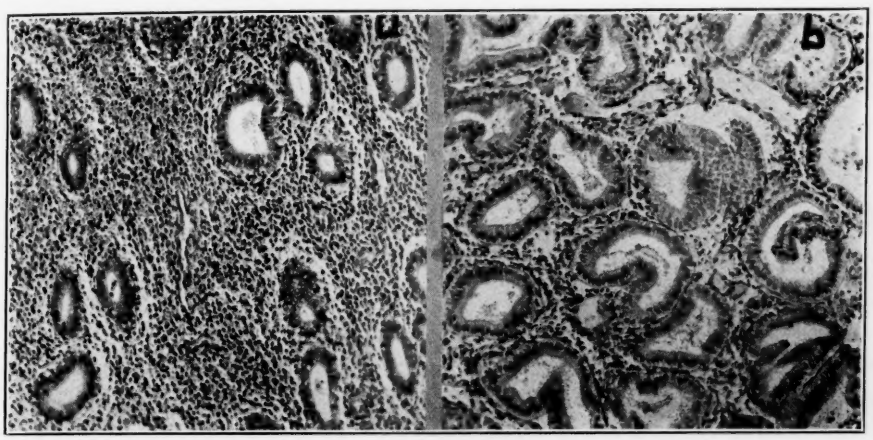

Fig. 5.—Case B. H. (*a*) Curette specimen during menorrhagia, showing low intensity of estrin action. (*b*) Biopsy in fourth week, after therapy, showing full effect of progestin.

B. H. was referred at age of 17 because of irregular and excessive flows of five days to three months, intervals being highly variable since the menarche at 15. There were also nervous irritability, headaches, tendency to weeping, and breast pains. The basal metabolism was 6 per cent below the standard. Pelvic examination revealed a small and retroverted uterus, which was held up by a pessary for the following four months. The right ovary was enlarged and cystic. Curettage on the nineteenth day of a flow served to stop the flowing. The tissue obtained showed a low intensity of estrogenic hormone stimulation of endometrium (Fig. 5, *a*). When, therefore, menorrhagia recurred a few months later after two long periods of amenorrhea, it was concluded that the therapy indicated was stimulation of underactive ovaries. The use of 5 doses of 25 units each of prephysin during each cycle for the next year was followed by essentially regular four-week cycles with moderate flow. Treatment was suspended, and endometrial biopsy showed a well-developed progestin effect on the twenty-second day of a twenty-six-day cycle (Fig. 5, *b*). For 10 cycles without therapy menses continued satisfactorily regular, to be followed by longer cycles and recurrence of menorrhagia. It was therefore deemed wise to return at once to the type of therapy which had succeeded in the previous year. Symptoms, which had been relieved, were not severe. Pelvic examination at this time showed that the cystic ovary was no longer palpably enlarged.

Consideration of these three cases of menorrhagia, with checking of excessive flow, improvement in rhythm, and evidence of the formation

of a corpus luteum after treatment, makes it evident that gonadotropic pituitary materials applied to the human being may be the cause of complete ovulatory cycles, and improvement in ovarian function. The necessity for indefinite continuation of such treatment cannot yet be settled. Results to date make it appear that sustained treatment will be found necessary, as might be expected, since this is substitutional pituitary therapy, without reason to expect a cure. In two of the most successful cases mentioned, as in others, we have found "antihormones" present in the blood after treatment had been carried on for some months, but the clinical progress was apparently not impeded, nor were anaphylactic phenomena observed with continued use of the pituitary extracts.[5]

STERILITY

Obviously the most complete test of pituitary and ovarian function is fertility. Of the women who were treated primarily for relief of sterility three are illustrative of the problems to be met.

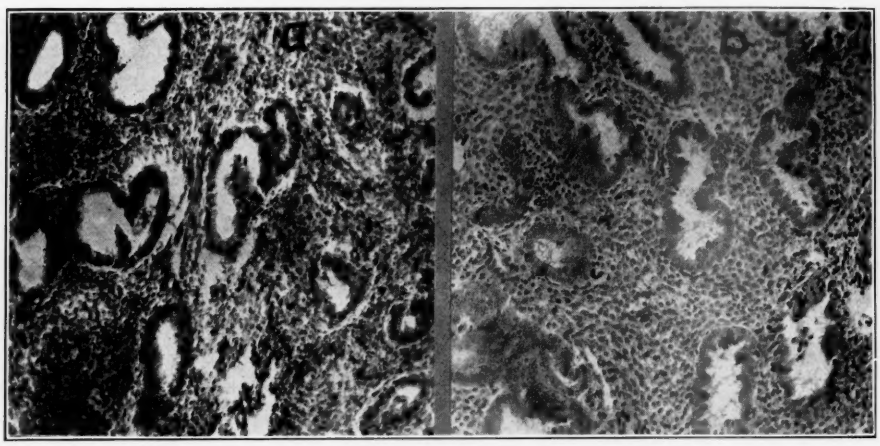

Fig. 6.—(*a*) Case R. J. Biopsy on twenty-third day of forty-one-day cycle, showing poor estrin activity, with irregular shapes and sizes of glands. Pregnancy followed therapy. (*b*) Case S. N. Biopsy on twenty-eighth day of seven-week cycle, showing irregular glands, roughly simulating progestational effects, but with cellular characteristics of estrin action only. Pregnancy followed therapy.

R. J. was first seen at the age of 26 because of irregular and infrequent menses and sterility. Basal metabolism was within normal limits. She returned again at the age of 34 for the same reasons. Menstrual intervals were one to twelve months. Trial of thyroid had exaggerated nervousness. Some of the symptoms suggested a climacteric, and these were abated by the use of estrin (amniotin). This was discontinued after a few months. At the age of 38 she was seen again, when menses were occurring at four- to eight-week intervals. Endometrium obtained on the twenty-third day of a forty-one-day cycle showed glands of varying sizes, some dilated, but suggesting throughout the sections a low intensity of activity (Fig. 6, *a*). A retroversion, not previously present, was corrected with a pessary. Prephysin was used in 25-unit doses during the next 3 cycles, a total of only 18 doses being taken. Because of painful local reactions from the injections (early preparation, relatively crude), the treatment was discontinued. The next cycle was ended by a flow of only one day, and the patient reported nausea and breast symptoms very soon thereafter. A Friedman test made the diagnosis of pregnancy positive. Pregnancy was uneventful,

and was followed after two more years by a second successful pregnancy, with no more pituitary therapy.

The amount of therapy employed seems too small to account for the successful result, but the history and endometrial findings demonstrate that there was ovarian underactivity until pituitary treatment was used.

L. H. was seen at the age of 17 because of hirsutism and scanty flows of three to four days at six- to seven-week intervals. Use of thyroid, theelin, and emmenin produced no improvement. Amenorrhea for periods of five to twelve months were recorded, and pregnancy urine concentrate (follutein) was used, with 4 flows in six months. At this time the uterus was found to be distinctly infantile. She was married at the age of 18. After two years without treatment, at age of 20, the patient still had cycles at intervals of six to seven months, and was not able to become pregnant. Hypodermic injection of prephysin was started, using 25 unit doses for five days in the early part of each cycle. After 5 cycles, an endometrial biopsy was obtained, revealing only estrogenic hormone activity (Fig. 7, *a*), but followed six days later by a menstrual flow. The treatment was resumed, the number of doses increased to 10. Long menstrual intervals were decreasing, but regularity was not yet achieved. A second biopsy late in the fourth week of a cycle without treatment

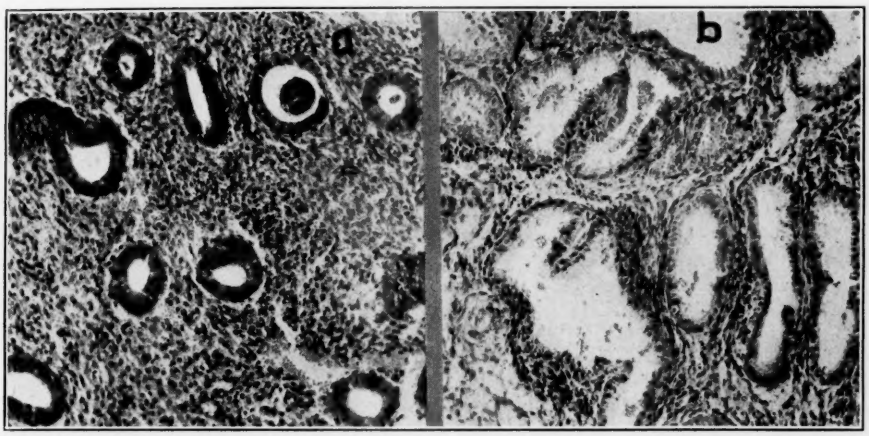

Fig. 7.—Case L. H. (*a*) Biopsy on twenty-second day of twenty-eight-day cycle, with inadequate estrin activity. (*b*) Biopsy on twenty-fifth day of twenty-seven-day cycle after therapy, showing later results of progestin action.

revealed a well-developed progestational endometrium (Fig. 7, *b*). Treatment was continued in a somewhat irregular fashion for 4 more cycles, and after twelve weeks' amenorrhea an Aschheim-Zondek test demonstrated pregnancy. The patient went to term, and has a healthy child. After two more years without treatment menses have continued at thirty- to thirty-nine-day intervals without periods of amenorrhea, but without further test of fertility.

S. N. came for examination at the age of 33 because of loss of fertility after the birth of a first child at the age of 31 years. Menses had varied from one to three months in interval, five days' duration, with aching dysmenorrhea since the pregnancy. There were many climacteric symptoms present. A tendency to obesity had developed, accompanied by acne. The basal rate was 16 per cent above the normal. Pelvic examination discovered cystic and enlarged ovaries and a retroverted uterus, which was corrected by pessary. The endometrium obtained on the twenty-eighth day of a 7-week cycle showed a very low grade of estrogenic activity, without evidence of progestin action (Fig. 6, *b*). The patient was therefore started on hypodermic injections of gonadotropic material from pregnant mare serum (Gonadogen, Upjohn). After the use of 18 doses of 10 units each, the amenorrhea of ten weeks was shown to be due to pregnancy, and she delivered a healthy second child at term.

The amount of treatment seems too small to be responsible for the result, but the tissue showed distinctly that the ovarian activity was below expected levels, and the mechanical replacement of the uterus can hardly be held accountable for the entire result.

Results are not always so easily accomplished. Failure has been encountered, for example, in an otherwise healthy woman of 27 years, where endometrial biopsy on the twenty-fifth day of a twenty-seven-day cycle showed a poorly developed estrogenic hormone effect, followed by anovulatory bleeding. Increasing doses of prephysin to the point of 20 injections of 100 units each in a single cycle failed to make any definite increase in the intensity of the estrogenic influence on the vaginal epithelium. It was concluded that the ovaries were not susceptible of stimulation by the means available, as in the case of Z. R. reported in the first section of this paper.

A puzzling case is that of I. T., referred at age of 35 years because of sterility, followed by six months' amenorrhea after a long period of years with four-week type of menstruation. The husband has, of course, been examined and found to produce large numbers of motile sperm. Physical examination and history gave no unusual findings, and pelvic examination was not unusual. The study of vaginal epithelium showed low intensity of estrogenic hormone activity. Gonadogen was given in 20 unit doses, 5 times in the first two weeks of the cycles, with improvement in regularity of flow but little increase in estrogenic response shown in the vagina. After two cycles with increase to 15 daily doses of Gonadogen there was more evidence of estrin action. During the fourth week of the cycle twenty-four-hour urine specimens were examined and found to contain 45 mg. pregnandiol glycuronidate in seven days, within normal expectations. Treatment was a bit irregular, amenorrhea occurred, but Aschheim-Zondek test made pregnancy unlikely, and the injections were resumed. The estrin activity continues to follow the treatment, sometimes approaching, but not equalling the normal expectancy of the second week of the cycle. Nevertheless five months' amenorrhea, without pregnancy leaves an unsatisfactory result. The problem is to determine the exact dosage needed to re-establish normal intensity of ovarian action. This may be beyond clinical judgment with present methods for quantitative estimation of the needs.

PRIMARY AMENORRHEA

Complete absence of menstrual function in an adult woman presents not only a test of the adequacy of gonadotropic therapy, but also the problem of determining whether the deficiency is due to lack of pituitary stimulation or lack of ovarian tissue which can respond to the stimulus. The methods already described can contribute to decisions on both aspects of the problem, as shown by the following two cases.

N. S. was admitted to the psychiatric service at age of 25 because of numerous phobias, and a complicated personality problem involving great reticence about sex matters, extending even to refusal to permit bimanual pelvic examination by a woman physician. There had never been a menstrual flow. Acne, obesity, small breasts, and a masculine escutcheon were the only important physical findings. The basal rate was 8 per cent above normal. A woman assistant finally won her confidence sufficiently to secure vaginal epithelium samples with a pipette. These showed cells and debris typical of the castrate condition (Fig. 8, *a*). It was not certain that there were any ovaries. She was given 15 daily doses of 25 units each of prephysin, during which time a marked change appeared in the vaginal material, including the occurrence of reduced numbers of leucocytes, less mucus and debris, and the desquamation of typical cornified cells (Fig. 8, *b*). There was a flow of blood stained material for one week, beginning five days after this series was completed. During this period of treatment, there was a marked improvement in the psychic condition, which has continued subsequently, making it possible for the patient to secure and keep employment.

Similar treatment was continued at home for 6 series of prephysin injections, but only a slight flow occurred, for one day on the twenty-second day after the first had appeared. Eight months later, on request, the patient returned and permitted examination under anesthesia, and the uterus was found to be small. Tissue obtained by curette showed low intensity of estrogenic stimulation, resembling the "Swiss cheese" hyperplasia with irregularly dilated glands in some areas (Fig. 8, *d*). There were two brief flows ten and seventeen days later, after resuming use of prephysin in 100 unit doses. The immediate result of this stimulation was not greater,

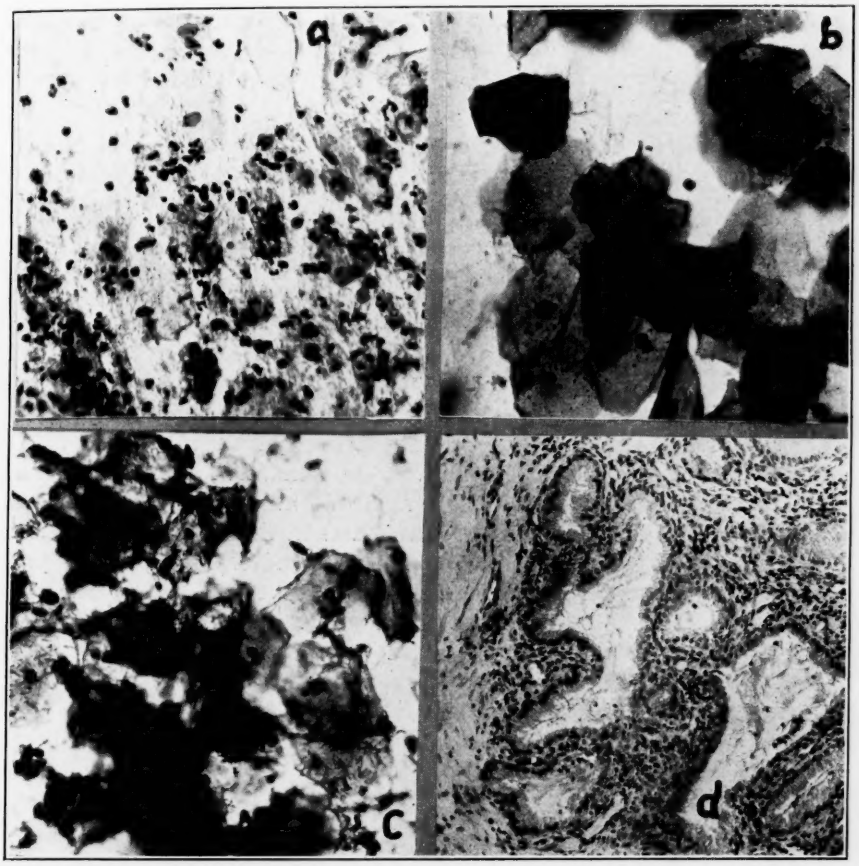

Fig. 8.—Case N. S. (*a*) Vaginal smear before therapy, showing the small deep layer cells, leucocytes, degenerating epithelial cells and debris. (*b*) Smear after ten days' treatment with prephysin, showing production of normal type vaginal squamous cells; beginning of cornification, and clearing of the field. (*c*) Smear taken after three months without treatment, showing some regression but presence of superficial type cells demonstrating continued low intensity of estrin action. (*d*) Biopsy obtained at same time as (*c*), showing irregular size and shape of glands in endometrium, from low intensity, sustained estrin action.

judged by vaginal epithelium, than the first use of 25 unit doses. In spite of 6 cycles of monthly treatment, using 10 and later 15 doses of 100 units each, the tissue response was not improved, but there was sustained psychic development toward a healthy attitude. After three months without treatment the vaginal reaction still showed some evidence of activity, and treatment was resumed using the gonadotropic pituitary extract of Armour, 300 Collip units per c.c. daily for fifteen days. With the use of this preparation subjective improvement was resumed about as promptly as with the previous use of prephysin. To date no further flows have

appeared. So far 4 flows have occurred in nineteen months, not a perfect record, but there has been obvious psychic improvement, the breasts have begun to develop, and it has been proved that there is ovarian tissue which can respond to artificial stimulation. The value of continued treatment is questionable. One can hardly hope to produce development to the point of fertility, and this may not be desirable. The social value of the results so far make the therapy worth while from both the point of view of the patient and the physician.

G. F. requested advice at age of 20 because of primary amenorrhea. Her only other complaints were of hot flashes, occasional vertigo, and small breasts. Basal metabolism was 6 per cent above the normal level. Under anesthesia the uterus was found to be small and retroverted. No endometrium could be obtained with a curette. She was started at once on use of 100 unit doses of prephysin daily for ten days, followed by similar doses on alternate days for twenty days. This series was repeated for 5 cycles without subjective change. The only alteration in the vaginal epithelium was the apparance of "mucified" cells on two occasions. No flow was recognized. Therapy was changed to the use of gonadogen, 10 unit doses given daily. The result was a more definite stimulation as judged by slight cornification of vaginal cells, and a brief menstrual flow appeared after the second series of 10 doses of 20 units each. The response, although slow in appearing, demonstrates again the presence of ovarian tissue which can be stimulated. Large doses and sustained therapy are required. Continued use of series of 20 doses, totaling 300 units, given over periods of twenty-five days, repeated each month, has failed to induce further flowing, or more marked vaginal epithelial cell response.

DISCUSSION

As instruments for diagnostic study and the estimation of the progress under therapy, the curette and the biopsy punch have advantages which make each of them necessary. For elimination of neoplastic disease the curette is indispensable. With infantile uteri the curette is still the only way to secure tissue at times. But in making examinations where the progress of the cycle is not to be interrupted, where prolonged hospitalization is impossible, or where repeated examinations are desired the biopsy technique is superior. We have not yet seen significant differences between biopsy specimens taken at different areas *above the cervix* at the same sitting. There is more variation between specimens taken at different depths beneath the lumen of the uterus. With attention to this feature, there is little risk of mistaking the effects of estrin and progestin in the endometrial glands.

The Papanicolaou and Shorr technique[2] for examining vaginal epithelium gives information similar to that obtainable by the vaginal biopsy method of Davis,[6] but with obvious advantages. Specimens are taken frequently by the patients, and brought in for examination. This makes possible study of changes from day to day when desired. The results are interpretable only in terms of estrin action, without evidence of progestin effect. To meet this deficiency the use of the pregnandiol determination in serial twenty-four-hour urine specimens is the best method, unless endometrial biopsies are obtainable. The biopsy approach is easier for the gynecologist, requires less laboratory time, but is frequently not welcomed by the patient. One further great advantage of pregnandiol estimation is the possibility of quantitative determination of the intensity of progestin secretion. It is difficult to estimate deficiencies of estrin or progestin action from the study of the biopsy specimens unless gross deficiency exists. Probably the success of a program

of treatment will be found increasingly to depend on the quantitative criteria for estimating progress. This has been the case in other endocrine disorders, such as thyroid deficiency, diabetes mellitus, tetany, and the climacteric.

The results presented at this time are selected from the patients studied for a sufficiently long time to make possible some judgment as to the adequacy of therapy. It will be evident that progress could have been measured more definitely and decisions made sooner in some cases if the vaginal epithelium and pregnandiol techniques had been freely available in the earlier years. More frequent use of biopsies has been limited by the cost of hospitalization for the purpose. Increasing experience with this technique, with no unfortunate consequences after hundreds of biopsies, makes office biopsy by experienced gynecologists a safe procedure.

We are still of the opinion that diagnoses as to the cause of amenorrhea, irregular menses, menorrhagia, and sterility cannot be made by any combination of history taking, physical examination, and pelvic examination, with ordinary laboratory tests. The use of the microscopic study of endometrium, or at times of the vaginal epithelium and the pregnandiol excretion give information of prime importance. Without such data diagnoses are inaccurate, and therapy is empirical. Such examinations are to precede the use of expensive and potent endocrine materials. To determine progress the history of menstrual flowing is likewise inadequate, unless fortified with similar examinations.

It is still all too evident that the need is for more potent as well as purified pituitary preparations. Some cases respond sufficiently to the extracts now available. As these quantitative concepts of ovarian activity are applied to individual cases it will become easier to vary treatment to fit the patient's needs, and also to decide at an early date which patients will probably not benefit from endocrine therapy.

There has been too little experience to judge the relative merits of the various pituitary preparations we have employed. Our major experience has been with prephysin (Chappel Laboratory). This is made from sheep and horse pituitaries. A small experience with gonadotropic antuitrin (Parke, Davis and Co.) reveals that this is active, but too low in potency for most uses. It is a hog pituitary extract, not yet released for sale. The trials of gonadogen (Upjohn Laboratory) have been distinctly encouraging. This is a preparation from the serum of pregnant mares, standardized in a large unit, which makes comparison with the other materials difficult. It has the advantage of being a dry preparation of great permanence, readily dissolved for injection, and so well purified that it causes less local reaction than other gonadotropic materials. Our use of the gonadotropic extract (Armour Laboratories) is too recent to warrant anything except the statement that it is apparently a safe material. The unit of standardization (Collip) is roughly one-tenth that used for prephysin. Large numbers of units must therefore be employed to secure clinical results.

We have deliberately presented cases demonstrating success, partial success, and failure following endocrine treatment. This series does

illustrate what may be expected from endocrine therapy in properly selected cases. These methods avoid both the ordinary hazards of surgery and the dangers of loss of function from the removal of ovarian and uterine tissue so often considered necessary in treating menorrhagia in the past.

SUMMARY

From an experience with use of genuine pituitary gonadotropic extracts for seven years, we are reporting examples of the results which may be expected in treating women for primary or secondary amenorrhea, for menorrhagia and irregularity of menstrual cycles, and for relief of sterility. All the syndromes presented here are considered to be the result of underactivity of ovarian hormones, dependent presumably upon underactivity of the anterior pituitary in supplying gonadotropic hormones. For accurate diagnoses and conduct of treatment the use of endometrial biopsy and vaginal epithelial samples secured by pipette, as well as of pregnandiol determinations in urine, are shown to be important aids. If these aids fail to show definite response to treatment, even though menstrual flows are occurring at fairly regular intervals, the treatment may well be increased or abandoned. The use of long series of repeated daily doses, extending for five to 15 days at the beginning of each menstrual cycle, seems necessary and is demonstrated to be safe. Results are not achieved in a single month. This study indicates the need for individualization of dose, and for the preparation of more concentrated pituitary extracts.

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Seegar, G. Emory: Ovarian Dysgerminoma, Arch. Surg. **37:** 697, 1938.

From a study of 79 cases of dysgerminoma reported in the literature and investigation of 19 instances available in the laboratory of Johns Hopkins Hospital, the author concludes that this newgrowth, representing less than 3 per cent of all malignant ovarian tumors, is relatively rare. It occurs in young persons usually under 30 years of age. It appears as a rapidly growing elastic, nodular mass in the adnexal region. In the more malignant types the retroperitoneal glands, peritoneum, omentum, bladder and rectum rapidly become involved through metastases, which rarely appear in distant organs. Dysgerminoma may be associated with other forms of ovarian tumor.

These newgrowths have a mortality between 35 and 60 per cent, with a slightly higher rate of recurrence and metastasis.

The treatment of choice is removal of the growth with adjoining tube. If removal is impossible the patient should be given the benefit of irradiation.

HUGO EHRENFEST

VARIATIONS OF LIPOID CONTENT IN CERTAIN OVARIAN TUMORS*

R. B. Greenblatt, M.D., Augusta, Ga., J. P. Greenhill, M.D., Chicago, Ill., and W. R. Brown, Ph.D., Augusta, Ga.

(From the Department of Obstetrics and Gynecology, Loyola University Medical School, Chicago, Illinois and the Departments of Pathology and Gynecology; and the Department of Bio-Chemistry, University of Georgia School of Medicine, Augusta, Ga.)

INTRODUCTION

THUS far, chemical investigations of tumors have detected little that indicates any marked deviation of the chemical processes of tumor cells from those of normal cells of similar origin. This is significant particularly when it is coupled with the fact that tumor cells have the capacity to produce complicated products of metabolic action specific for the parent cells from which they arose. Witness adenomas of the islets of Langerhans or metastatic carcinoma of the thyroid.

In applying these principles to the study of lipoids in certain ovarian tumors, much information may be gained, which, if properly evaluated, may become an open sesame permitting inquiry into the very origin of tumor cells. For here in these ovarian neoplasms the tumor cells seem to contain the same fats, lipoids, and chemical (hormonal) activity as the normal cells from which the tumors arose.

We, therefore, present this study in which allusion is made to the content and distribution of fats and lipoids in a group of ovarian tumors.

LIPOIDS IN GRANULOSA CELL TUMORS

Case 1.—Fig. 1 is a frozen section from a mature homogeneous type of granulosa cell tumor, stained with sudan III and hematoxylin. Note the island of granulosa cells with its striking periepithelial garland of lipoid laden stroma cells. The granulosa cells contain very minute protoplasmic sudanophilic droplets. Deposited in the connective tissue core that here and there invaginates the epithelial plug of granulosa cells are occasional aggregates of large coarse lipoid droplets. The cells of the connective tissue stroma immediately adjacent to the epithelial mass are large, swollen, heavily laden with very fine intensively staining sudanophilic granules and droplets. This thecalike reaction of the stroma suggests the probability that granulosa cells exert a profound influence on the connective tissue immediately in contact with it. The chemical activity (hormonal) of the neoplastic granulosa cells, as reflected by its lipoid deposition, is analogous to the normal maturing follicle just prior to rupture when the granulosa cells show but minimal luteinization in contrast with the abundant lipoid accumulation in the theca interna.

Case 2.—Fig. 2 is a frozen section from an immature trabecular type of granulosa cell tumor stained with sudan III and hematoxylin. The illustration shows the partial condensation of the solid masses of mesenchyme into trabecular structures. The lipoid distribution follows no particular pattern. Large globules of fused fat droplets are found extra- and intracellularly here and there among the cells comprising the immature trabeculae. The undifferentiated connective tissue stroma shows a nondescript minimal scattering of lipoid droplets. The lipoids when studied with the polariscope are nonerystalline and non-refractile although

*Presented before the Chicago Gynecological Society, October 21, 1938.

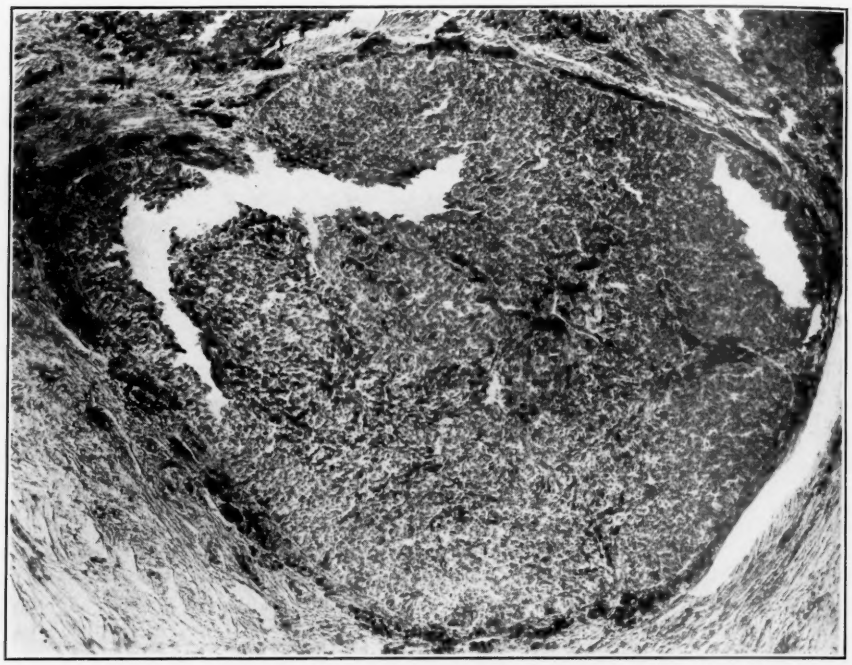

Fig. 1.—Case 1. Granulosa cell tumor (mature homogeneous type). Note the periepithelial accumulation of lipoids (stained black) in the stroma simulating a thecalike reaction. (Sudan III-hematoxylin stained frozen section ×150.)

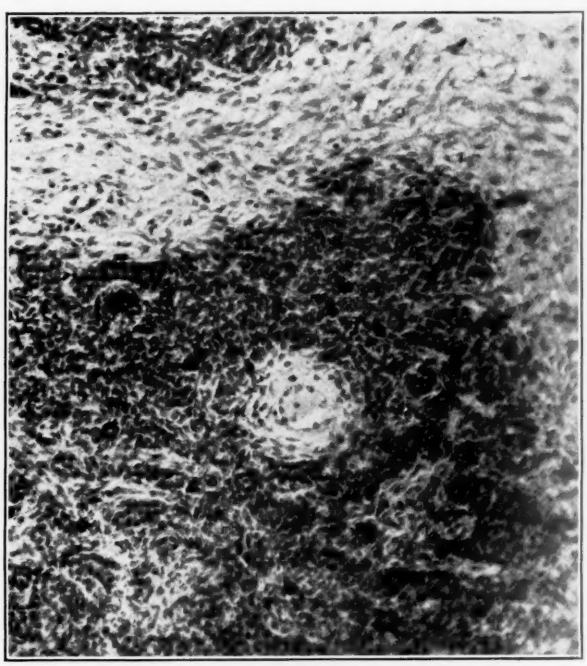

Fig. 2.—Case 2. Granulosa cell tumor (immature trabecular type). Note the lipoid distribution (black globules). (Sudan III-hematoxylin stained frozen section ×280.)

an occasional birefringent crystal is observed. The lipoids in this tumor are quite variable, for their presence is not encountered in all sections under study.

LIPOIDS IN THECA CELL TUMOR

CASE 3.—Fig. 3 is a frozen section from a thecoma stained with sudan III and hematoxylin. This illustration typifies the lipoid distribution in truly luteinized (pseudo) theca cell tumors. Large sheaves of connective tissue cells are surcharged with intracellular sudanophilic granules. Occasionally the lipoids are in the form of larger droplets, some of which may be found extracellularly. The intensity of the lipoid accumulation as brought out by the sudan-staining reaction varies in different areas of the same tumor. Some sheaves contain moderate to negligible amounts of sudanophilic lipoids. The dense white fibrous connective tissue core forms the matrix of the tumor. This may be abundant, altogether lacking, or comprise the greater part of the tumor. The lipoids are frequently more abundant

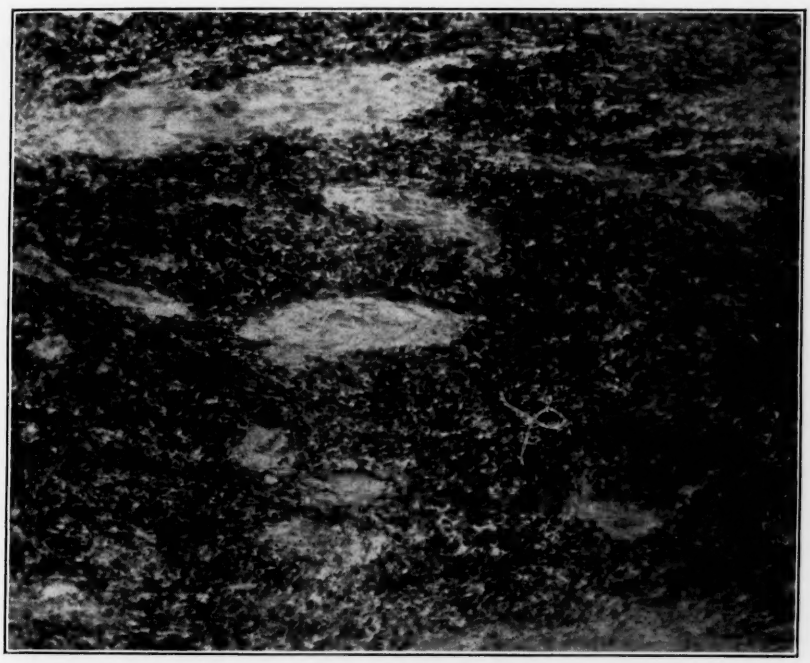

Fig. 3.—Case 3. Theca cell tumor. Note the sudanophilic droplets stained black in illustration. (Sudan III-hematoxylin stained frozen section low power.)

where the fibrillar connective tissue cells take on a plump fusiform epithelioid character. The fats, when studied with the polarizing microscope, show a marked abundance of refractile lipoids. They are for the greater part doubly refractile, i. e., anisotropic lipoids; biaxial, and show oblique extinction.

In the normal ovary the counterpart of the cellular component of this tumor is found in the proliferating connective tissue that takes on thecalike properties in the formation of an atretic follicle or in the cells of the theca interna participating in corpus luteum formation. Because of the intense sudanophilic character of the lipoids and the desmogenic nature of the constituent cells, these tumors have been designated xanthofibroma theca cellulare.

CASE 4.—Fig. 4 is a frozen section stained with hematoxylin and sudan III from a "theca-granulosa" cell tumor previously reported by us (J. P. G. and R. B. G.)[1] in this JOURNAL. The epithelial plug of granulosa cells contains a comparatively meager amount of lipochromic granules. The stroma in juxtaposition to this mass

of granulosa cells shows marked sudanophilic accumulation. Surrounding the epithelial nest is a broad zone of fibromatous tissue composed of plump fusiform cells, which in part is so intensely sudanophilic that on gross inspection of the section it appears as a massive tomato red area in color. On studying these sections with the polarizing microscope, an abundance of refractile lipoids is found in the fibromatoid part of the tumor; these are, for the greater part, birefringent. Most of the birefractile crystals are biaxial and show oblique extinction; a few show parallel extinction. The fats in the epithelial plugs show a smaller amount of refractile lipoids, but these are mostly isotropic. Here side by side are neoplastic granulosa and theca cell components in the same tumor, the counterpart of which is to be found in the normal ovary, in the ripening Graafian follicle with its periepithelial garland of theca cells. That granulosa-theca cell tumors

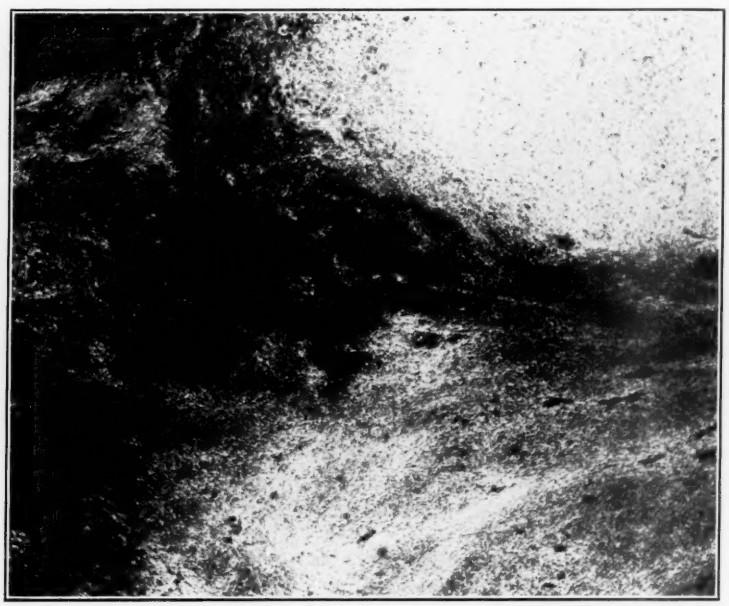

Fig. 4.—Case 4. Granulosa-theca cell tumor. Note dense sudanophilic fibromatoid tissue surrounding a focal mass of granulosa cells (upper left). (Sudan III-hematoxylin stained frozen section ×135.)

occur more frequently than is at present appreciated is quite probable, for in the embryonic development of the ovary, granulosa cells are formed in loco from ovarian mesenchyme as are likewise the thecal and stromal tissue. In 1882 Maffucci recorded the details of an ovarian tumor in which granulosa and theca cells were predominant.[2]

LIPOIDS IN ARRHENOBLASTOMA

Case 5.—Fig. 5 is a frozen section of the trabeculated type of arrhenoblastoma stained with sudan III and hematoxylin. The mesenchyme attempts to form germinal cords; lipoid deposition in the tumor is limited to the Leydig cells accompanying the cords. The prototype of this tumor may be found in the male fetus as early as five and six months when the Leydig cells laden with fat accompanying the trabeculae make their appearance in the male gonad. The lipoids in arrhenoblastoma are limited in a great measure to the cytoplasm of the Leydig cells. Only a small part of these fats are refractile, and these are usually birefringent, showing oblique extinction.

LIPOIDS IN HYPERNEPHROMA OF THE OVARY

CASE 6.—Fig. 6 is a frozen section from a hypernephroma of the ovary stained with sudan III and hematoxylin. This neoplasm is very cellular. Large sinusoids demarcate the tumor into large cellular zones. The constituent cell is large with a proportionately large nucleus and nucleolus. The cytoplasm is spongy, containing an abundance of sudanophilic lipoids. The distribution of the lipoids, however,

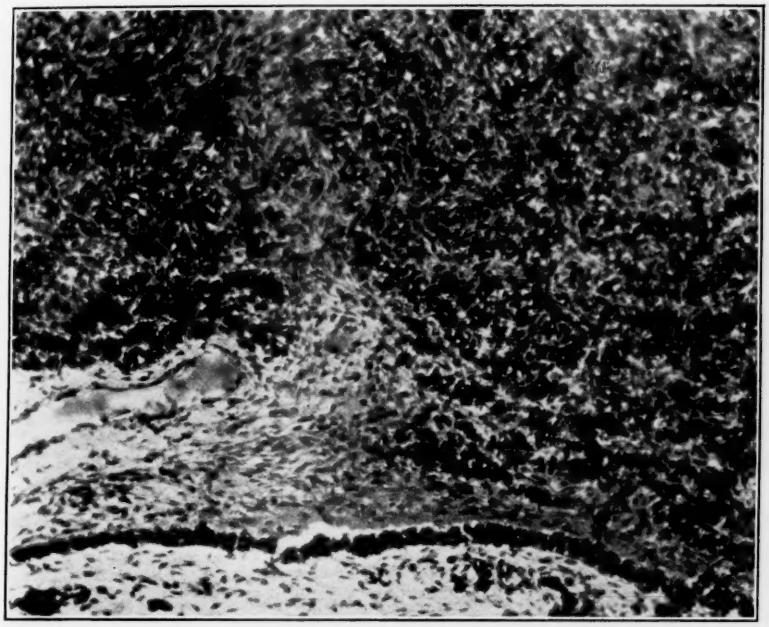

Fig. 5.—Case 5. Arrhenoblastoma—trabecular type. Sudanophilic Leydig cells accompany the condensation of the mesenchyma into cordlike structures. (Sudan III-hematoxylin stained frozen section ×240.) (Courtesy of W. Schiller.)

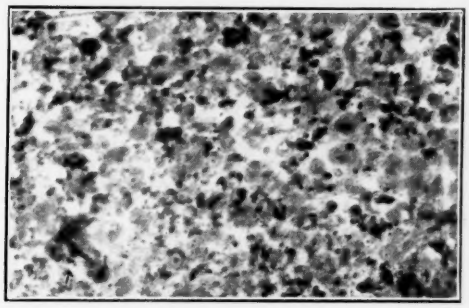

Fig. 6.—Case 6. Hypernephroma of ovary. Note the lipoid distribution. Arrow points to typical lipoid crystals found in abundance in this tumor. (Sudan III-hematoxylin stained frozen section ×300.)

is very irregular, being more pronounced in the vicinity of the sinusoids. The fat is in the form of large, bright red lipoid cytoplasmic globules, or large, bright yellow extracellular lipoid crystals. The latter are particularly noteworthy; they appear to be oblong acicular crystals, arranged in bizarre fashion, frequently in fasciculated bundles or piled upon one another to give a laminated appearance, or arranged in groups at an obtuse angle. Some of these are well illustrated near the left border in Fig. 6. The sections when studied with the polarizing microscope exhibit an abundance of refractile lipoids. Some of the large crystals just

described are isotropic; the larger number, however, are doubly refractile and show biaxial oblique extinction. When stained with Nile blue, the cytoplasmic globules are royal blue and the extracellular crystals pinkish yellow.

In the classification of this neoplasm much controversy exists. Opinions confine it to the luteinizing granulosa cell tumors, the luteomas or the hypernephromas. Sections of normal corpus luteum, adrenal, hypernephroma of the kidney and suprarenal cortical adenoma were studied with sudan III and Nile blue stains. It is worthy of note that only in the suprarenal cortical adenoma are there to be found lipoid crystals that are identical with those observed in the hypernephroma of the ovary. The Nile blue stain brings forth an abundance of similar pinkish yellow crystals. These crystals, that are peculiar to both the hypernephroma of the ovary and suprarenal cortical adenoma, not only have comparative morphologic features and staining reactions, but also identical polariscopic characteristics. The lipoid study of this tumor supports the contention that its cells are derived from misplaced suprarenal nests in the ovary.

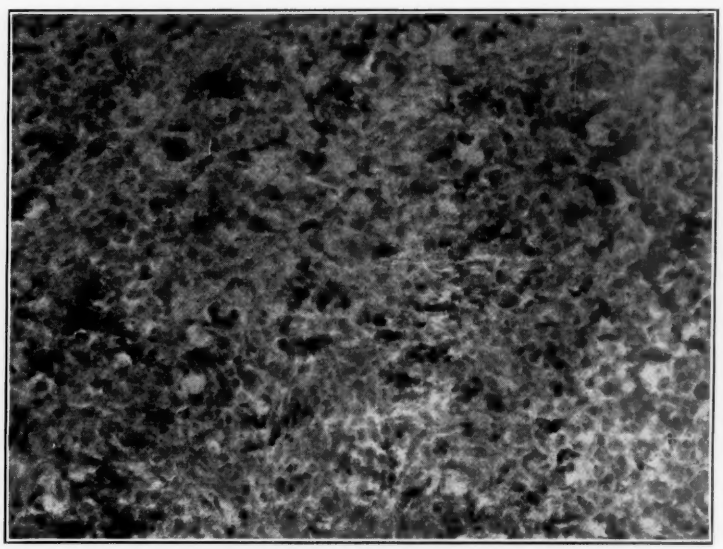

Fig. 7.—Case 7. Krukenberg tumor. Note abundance of lipoids present. (Sudan III-hematoxylin stained frozen section ×300.)

LIPOIDS IN A KRUKENBERG TUMOR

CASE 7.—Fig. 7 is a sudan III—hematoxylin stained section of a Krukenberg tumor. The lipoids are found haphazardly distributed and exist both as intra- and extracellular fat droplets. The fat, when studied with the polarizing microscope, proves to be nonrefractile. With the Mucicarmin stain an abundance of mucin distending the cytoplasm of the signet cells is apparent. Geist[3] recently pointed out that one so-called luteoma reported in the literature, that he had occasion to examine, turned out to be a Krukenberg tumor. It is evident that the error in diagnosis could be attributable to the large amount of lipoids present in this so-called luteoma to warrant the possibility of such a diagnosis. Since Krukenberg tumors may contain lipoids, this finding proves that lipoids are not a distinctive feature of the endocrine group of ovarian neoplasms.

LIPOIDS IN A FIBROMA

CASE 8.—Fig. 8 is a sudan III—hematoxylin stained section of an ovarian fibroma. The deposition of sudanophilic droplets is found particularly in the vicinity of nests of fibrous connective tissue cells rather than in the mature collagenized or hyalinized zones. Certain aspects in the clinical history of this case would

suggest the possibility of a thecoma. The patient had menorrhagia of two and one-half weeks' duration during each month with accompanying breast enlargement. After removal of this large unilateral tumor, the menses were reduced to a regular three-day flow, and the patient ceased to experience the cyclic breast enlargement. The great variation in the cellularity of the tumor, the collagenized zones, and the presence of fats in the tumor are also suggestive of thecoma. However, on polariscopic examination, the lipoids are nonrefractile, thus differing from the lipoids in theca cell tumors.

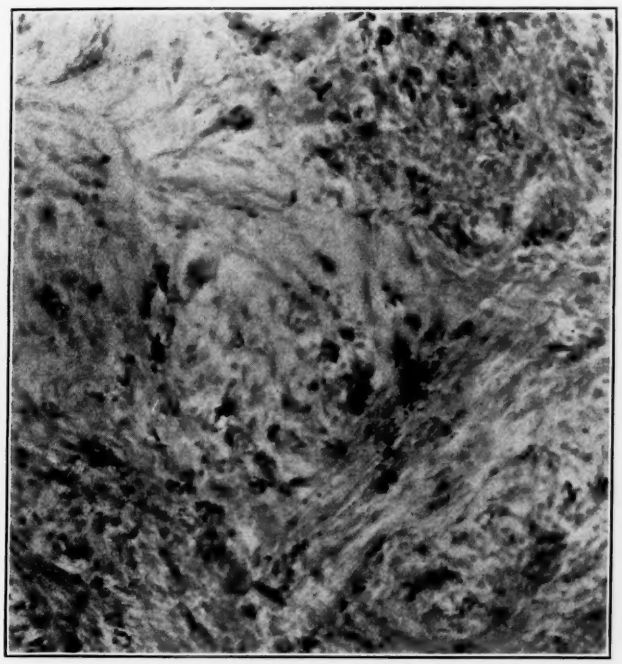

Fig. 8.—Case 8. Fibroma of the ovary. Note the lipoid deposition. (Sudan III-hematoxylin stained frozen section ×280.)

TECHNIQUE AND ANALYSIS

In an attempt to establish some basic facts concerning the lipoids in ovarian tumors, extractions and chemical analyses of the fat content were performed in eleven of the tumors in our series. Sections of tissue were taken from the best preserved portions of the tumor. The tissues were minced, weighed, and extracted for several hours, depending upon the size of the sample, with hot alcohol in a Sohxlet extraction apparatus. The alcohol extract was evaporated carefully to dryness and the residue extracted several times with small portions of ether. The ether extracts were combined, made to volume and an aliquot portion taken for analysis. The total lipoid material was determined by evaporating an aliquot portion of the ether extract and weighing the residue. This residue was taken up in chloroform. The chloroform extract was divided, one part being used for the determination of cholesterol, the remainder for the estimation of lipoid phosphorus.

In Table I, the term "total lipid" denotes the weight of the alcohol soluble material which was also soluble in ether. The "phospholipid"

values were arrived at by determining the total phosphorus in the chloroform extract above by the Briggs method. The amount of phosphorus was multiplied by 25.1 to get the charted values. Cholesterol was determined colorimetrically by the acetic anhydride method. The term "lipid residue" denotes the alcohol-ether soluble material not accounted for as cholesterol and phospholipid. In Table I the 11 tumors studied by chemical analysis are divided into 2 chemical groups. The incretory group (1 to 7) supposedly yields telltale evidence of some endocrine disturbance. In this group there are 4 granulosa cell tumors, 2 theca cell tumors, and 1 hypernephroma of the ovary. The nonincretory group (8 to 11) is supposedly without endocrine significance. In this group there are 2 fibromas, 1 Krukenberg tumor, and 1 probable rete cell tumor. It is noted that in the incretory group the phospholipid content ranges from 0.31 to 1.88 gm. per cent and the cholesterol levels from 0.34 to 1.27 gm. per cent of wet weight. One fact is singularly brought out by analysis of this table and that is the comparatively low values for phospholipid (0.08 to 0.27) and cholesterol (0.02 to 0.29) in the non-incretory group. These values unequivocally permit the division of these tumors into two clinical groups.

TABLE I. PERCENTAGE OF LIPOID MATERIAL

DESCRIPTION OF OVARIAN TUMORS	WEIGHT OF TISSUE GRAMS	TOTAL LIPID GRAMS	PER CENT OF WET WEIGHT			
			TOTAL LIPID	PHOSPHO-LIPID	CHOLES-TEROL	LIPOID RESIDUE
1. Granulosa cell (mature homogeneous)	0.57	0.024	4.21	0.78	0.46	3.00
2. Granulosa cell (mature homogeneous)	6.27	0.328	5.23	0.93	0.34	3.96
3. Granulosa cell (immature trabecular)	4.60	0.126	2.74	0.92	0.68	1.14
4. Granulosa cell (mature trabecular)	1.30	0.043	3.31	0.31	0.57	2.43
5. Thecoma (cellular)	0.79	0.039	4.94	0.60	1.05	3.28
6. Thecoma	2.11	0.040	1.89	1.19	0.41	0.29
7. Hypernephroma	0.97	0.035	3.63	1.88	1.27	0.48
8. Rete cell (?)	33.00	0.357	1.08	0.27	0.29	0.52
9. Krukenberg	57.10	2.452	4.29	0.23	0.29	3.77
10. Fibroma	44.10	0.144	0.33	0.08	0.02	0.23
11. Fibroma	50.80	0.336	0.66	0.22	0.12	0.31
Thecoma (Geist)	109.00	2.990	2.70	0.32	1.10	1.28

In evaluating the one thecoma chemically analyzed by Geist,[4] we find his rather high value for total cholesterol, i.e., 1.10 gm. per cent was matched by one of our thecomas, i.e., 1.05 gm. per cent when compared to the ratio of cholesterol to total weight of tissue. The fibromas under study showed lipoid accumulation when stained with sudan III and in a measure simulated thecomas morphologically. However, the polariscopic features of these lipoids and their low cholesterol values on chemical analysis rule out their consideration as thecomas.

The granulosa cell tumors listed in the table as 1 and 2 resembled each other morphologically, both being of the mature homogeneous type. Frozen sections stained with sudan III yielded similar reactions. It is significant that the close comparative values obtained on chemical analysis corresponded to their morphologic similarity.

DISCUSSION

In our series of solid ovarian tumors studied with special lipoid stains there were included granulosa cell tumors (5), theca cell tumors (2), arrhenoblastomas (4), disgerminomas (4), Brenner tumors (2), Krukenberg tumors (2), fibromas (5), fibromyomas (2), fibrosarcoma (1), adenocarcinomas (2), as well as a hypernephroma of the ovary, a combined granulosa-theca cell tumor, and a possible rete cell tumor of the ovary. It seemed that fat may be encountered in ovarian neoplasms (exclusive of dermoids and teratomas) in at least three distinct conditions: (1) as a degenerative process, (2) as an inherent capacity of certain embryonal mesodermal tissue, and (3) as a product of tissue metabolism (hormone storage).

In disgerminomas there may be found, in more or less abundant numbers, large macrophagic cells filled with sudanophilic lipoids. These cells appear more numerous in the vicinity of necrotic areas. The fat is nonrefractile and probably degenerative. In Krukenberg tumors, fibromas, fibromyomas, etc., the lipoid deposition may be marked and is present in the form of intra- and extracellular sudanophilic granules and droplets or large fused globules. Brenner tumors show a meager amount of fat and this is found in the fibromatous tissue as minute round lipochromic granules resembling streaks of fine reddish sand. About some of the squamous cell nests, these fine granules are occasionally more prominent. It appears that the lipoids in this group are part of a degenerative process.

The question arises as to what significance may be attached to the presence of lipoids in the incretory group of ovarian tumors. Does the presence of lipoids actually represent storage of hormones? The granulosa cell tumors not only vary greatly in their morphology but vary just as widely in their fat content, and yet have a predominantly similar clinical syndrome, that of estrogen stimulation. It has been assumed that granulosa cell tumors contain comparatively minor amounts of lipoids and that these are phospholipid in nature (Melnick and Kanter[5]). It has long been known that some granulosa cell tumors undergo extensive luteinization (pseudo). In 1910 Lécène[6] recognized a type of granulosa cell tumor rich in fats and lipoids, which he termed "folliculome lipidique." Moulonguet[7] and Plate[8] have reported similar cases. In Moulonguet's case there was an abundance of double refractile lipoids, i.e., cholesterol and cholesterol esters. Loeffler and Priesel[9] separated from the granulosa cell tumors, the xanthofibromas, a desmogenic group rich in lipoids. It has been shown that a goodly amount of the fats in this group, now commonly referred to as thecomas, is in the form of doubly refractile lipoids, i.e., cholesterol esters. In the combined granulosa-theca cell tumor re-

ported by us the doubly refractile fats were particularly abundant in the fibromatoid part of the tumor. It appears that both granulosa cell and theca cell tumors give more or less identical clinical syndromes in spite of the fact that on polariscopic study the amount of doubly refractile crystals may be minimal, or lacking in one and abundant in the other. The chemical analysis of these tumors, however, shows that both have quite an amount of total cholesterol, though this value tends to be much higher in theca cell tumors.

What influences the deposition of an abundance of lipoids in certain of the incretory tumors, and not in others? When granulosa cell tumors contain an abundance of lipoids they are spoken of as luteinized granulosa cell tumors. Theca cell tumors contain an abundance of lipoids, and by the same token are luteinized theca cell tumors. The evident corollary presents itself that theca cell tumors may well exist that are not luteinized, just as theca and potential theca cells exist in the normal ovary. In this series one fibrosarcoma of the ovary on microscopic study (in reality a very cellular fibroma) exhibited every characteristic that is generally attributed to the thecoma, except that with sudan III stain, lipoids were not demonstrable and clinically did not yield endocrine disturbances. Traut and Butterworth[10] have done some excellent experimental work on mice, and have suggested that there exists an undifferentiated (unluteinized) and a differentiated (luteinized) type of theca cell tumor. By irradiating the mouse ovaries these authors have produced granulosa cell tumors as well as so-called luteomas. They concluded, however, that "luteomas are formed by luteinization of the granulosa cell tumors thus produced."

One point should be made clear; the abundance of lipoid in the incretory tumors does not necessarily mean luteinization. Lipoid deposition and luteinization are not synonymous (Varangot[11]). Luteinization is mirrored in the endometrium by the production of a secretory phase. The endometrial studies in most of the thecomas, so-called lutein cell tumors (luteomas) and luteinized granulosa cell tumors have shown an excessive estrogenic effect, i.e., cystic glandular hyperplasia.

The lipoids in arrhenoblastoma follow a definite pattern. The lipoid accumulation is practically wholly confined to the Leydig cells accompanying the mesenchymal masses, cords, or tubules. The lipoids in the four cases studied with the polarizing microscope were identified for the greater part as nonrefractile, with but a small amount of birefringent crystals showing oblique extinction. In contrast to this finding we mention the case report of Gnassi[12] who found that "double refractile crystals were conspicuous in the interstitial cells."

Hypernephromas of the ovary have been the subject of much controversy. These tumors, like the suprarenal cortical adenomas, may be virilizing in their effect. The presence of a great abundance of morphologically similar isotropic and anisotropic lipoids of similar staining reactions with Nile blue sulfate and sudan III in both the suprarenal cortical adenoma and the hypernephroma of the ovary studied by us permits of a more than casuistic inference.

Some significance, therefore, can be attributed to the lipoids in ovarian tumors. The deposition of lipoids in the incretory group resembles the deposition of lipoids in the normally functioning ovary, i.e., in the luteinization of theca cells, in the accumulation of lipoid droplets in the granulosa cells of the maturing Graafian follicle, and the corpus luteum; or the lipoid deposition may correspond to that observed in the male gonad after the fifth month of fetal life. It is assumed that in the normal gonad, both male and female, lipoid deposition is a process closely linked with endocrine metabolism and hormone storage. May it not be surmised that the lipoids in the incretory group of ovarian tumors are a part of a similar process?

CONCLUSIONS

Tissue sections from 32 solid ovarian neoplasms were studied with sudan III and Nile blue sulfate stains to ascertain the lipoid distribution. From this series, eight cases were selected to illustrate the specific and nonspecific distribution of the lipoids.

Fat stained sections were studied with the polarizing microscope, to ascertain to what degree refractile and nonfractile lipoids were present. The refractile lipoids were studied for their isotropic and anisotropic qualities, as well as for their axial and biaxial features.

Extraction and chemical analysis of the fat content in 11 of the tumors were done. Determinations were made on total lipoid material, total cholesterol, and lipoid phosphorus. It was found that the incretory tumors differed from the nonincretory tumors, in that the former have a consistently greater phospholipid and cholesterol content than the latter.

The chemistry of tumor cells is very much like that of the normal cells from which they arise, particularly in regard to their lipoid storage and chemical metabolism. The application of this principle may prove of value in determining an acceptable classification of the ovarian neoplasms.

The authors gratefully acknowledge their indebtedness to Edgar R. Pund, Augusta, Ga., for kindly advice and assistance rendered during the execution of this work and to Walter Schiller for permission to use his sections of arrhenoblastoma. We wish to thank Otto Saphir, Chicago; Charles Geschicter, Baltimore; Joseph Riopelle, Montreal; J. Pritchard, Montreal; J. M. Neely, Lincoln, Neb.; M. J. Schlesinger, Boston, for sections of tissue, some of which were of extreme usefulness in this study, also to the Spencer Lens Co. for the petroscope employed.

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55 E. Washington Street, Chicago.
University of Georgia, Augusta, Ga.

DAILY GONADOTROPIC HORMONE TESTS DURING FIFTY COMPLETE MENSTRUAL CYCLES*

FRED E. D'AMOUR, PH.D., DOROTHY FUNK, M.A., AND HELEN LIVERMAN, M.A., DENVER, COLO.

(From the Research Laboratories of the University of Denver)

THE development in civilized man of a greater sense of responsibility toward the consequences of his sexual encounters has led to a demand for information which could be used in controlling such consequences. Since the survival period of egg and sperm is short, the time relationship between ovulation and the sex act is immediately apparent as a determining factor and the importance of knowing at what time during the menstrual cycle ovulation occurs is therefore obvious.

Many techniques have been used. Hartman, in his excellent volume, *Time of Ovulation in Women*,[1] describes these methods and evaluates the results. Although not considering the question definitely answered, he finds the evidence from all sources sufficiently confirmatory to justify the statement:

> "On the whole the best evidence points to a midinterval ovulation as the rule for the human species. As the more objective and reliable proofs accumulate, they show a trend decidedly toward a complete denial of ovulation in the last quarter of the cycle, i.e., toward the establishment of the Knaus-Ogino law. But thus far we cannot yet give this final approval. We still have a long way to go before we can brand as a falsehood a woman's assertion that she conceived in the so-called sterile period of the cycle. There is still insufficient data for any actuarial expert to base the cost of insurance that might be sold with a book advocating the safe period.
>
> "Nevertheless, the opponents of the safe period are more and more placed on the defensive as new facts accumulate."

We may accept the view, then, that ovulation in women occurs usually during the midinterval of the menstrual cycle. If, however, the question be altered to read: "Does ovulation occur *only* during the midinterval?" we do not find the evidence for an affirmative answer nearly as complete. Since the publications of Knaus and Ogino appeared, in which the principle of midinterval ovulation was most strongly established, many investigators have devoted their attention mainly to this portion of the cycle and have neglected the earlier and later parts. This is particularly true where the direct method, that of ovarian inspection at laparotomy, has been used. And a rather imposing number of workers (Stein and Cohen[2] cite ten) have expressed the view that extracyclic ovulation may occur, either spontaneously or as a result of coitus. In other words, while a mass of data support the view that ovulation *usually* occurs during the midinterval, there is no such wealth of evidence that it occurs *only* at that time.

In the present study we attempted to obtain information concerning the time of ovulation by testing the day-by-day urine excretion for gon-

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adotropic hormone during 50 complete menstrual cycles. Not nearly enough data have been obtained to justify any far-reaching conclusions, but we are convinced that at least the possibility of several ovulations occurring per cycle has been established. If this possibility is to be taken into account, future studies will have to be so conducted that every day of the cycle is considered of equal importance. For such studies the method of urinalysis seems best suited as no method can be used which makes too great demands upon the forbearance of the subject. Daily uterine biopsies, uterine motility tests, withdrawal of blood, to say nothing of laparotomies, are clearly out of the question. Whether a positive test for gonadotropic hormone indicates that ovulation is impending or has occurred will be discussed later.

Experimental.—Kurzrok[3] in 1934 reported a study in which the method of testing the urine for gonadotropic hormone was used. This method is a modified Aschheim-Zondek pregnancy test[4] in which an alcoholic precipitate from 66 c.c. of urine is injected into a mouse. We have carried out preliminary studies in which this method was employed except that rats were used. (Herein may lie the reason for our failure to duplicate Kurzrok's results, as the mouse may be a more sensitive animal. This is true of the gonadotropic substance in menopause urine, which our substance resembles. Vide infra.) In any case, three complete cycles were tested by this method, no positive reactions occurred; the amount of urine was then doubled, eleven cycles being tested, a few scattered positives appeared. The amount was then increased to 240 c.c. The precipitates from this amount of urine were frequently toxic and although three more cycles were tested no positive reactions were obtained. The method of Katzman and Doisy[5] was then employed on 13 cycles. Again a few positive reactions were found but many of the animals died, making the study incomplete. None of these cycles is included in the present report.

The method next adopted and which proved very satisfactory, was that of Levin and Tyndale,[6] in which tannic acid is used as the precipitating agent. Either twelve-hour nocturnal specimens or full twenty-four-hour samples were collected, the active principle obtained by precipitation and, in the case of twelve-hour samples the entire precipitate, in case of twenty-four-hour samples one-half the precipitate, injected into a twenty-six-day-old female rat. Injections were made daily for three days and the animals sacrificed at the end of one hundred hours. A test was considered to be positive if the weight of the ovaries was double that of those in control animals. As a matter of fact, there were very few cases where any doubt existed as to whether a reaction was positive or not, the average weight of the ovaries of positively reacting animals being 52.2 mg. while that of 253 control animals was only 10.7 mg. Usually a series of animals would be examined showing no evidence of ovarian stimulation whatever. The next animal would show a gaping vagina, heavy estrus smear, enlarged uterus and ovaries hyperemic, greatly enlarged and mulberry-like in appearance. Sometimes this reaction was still present in the following animal, usually, however, it lasted only one day and again a series of completely negative animals would be encountered. Nearly all positive ovaries were sectioned and studied microscopically. The precipitate was remarkably nontoxic although in a few cases an animal died. We were fortunate that in these rare cases one animal of the pair survived and each day of the cycles presented is represented by at least one, usually by two, animals. Toxic effects were noted only during the warm months. It is a weakness inherent in this study that the number of animals per test is not greater. However, after the discouraging results obtained using smaller amounts of urine, we believed that the concentration of gonadotropic substance was in no case very great and that it would be better to use large doses and obtain unequivocal positive reactions when they did appear than to distribute the material among a larger number of animals. At present we are using the uterine weight method of Levin and Tyndale.[7] This method is apparently more sensitive and permits the use of larger numbers of animals. It may be mentioned, however, that the total number used in this study, including the preliminary studies, exceeded 4,000.

RESULTS

The results are presented in Charts 1 and 2 and are summarized in Table I. We desired to take into account variations among individuals, and variations from month to month in the same individual. Five of the 12 subjects were therefore tested through from six to eleven consecutive

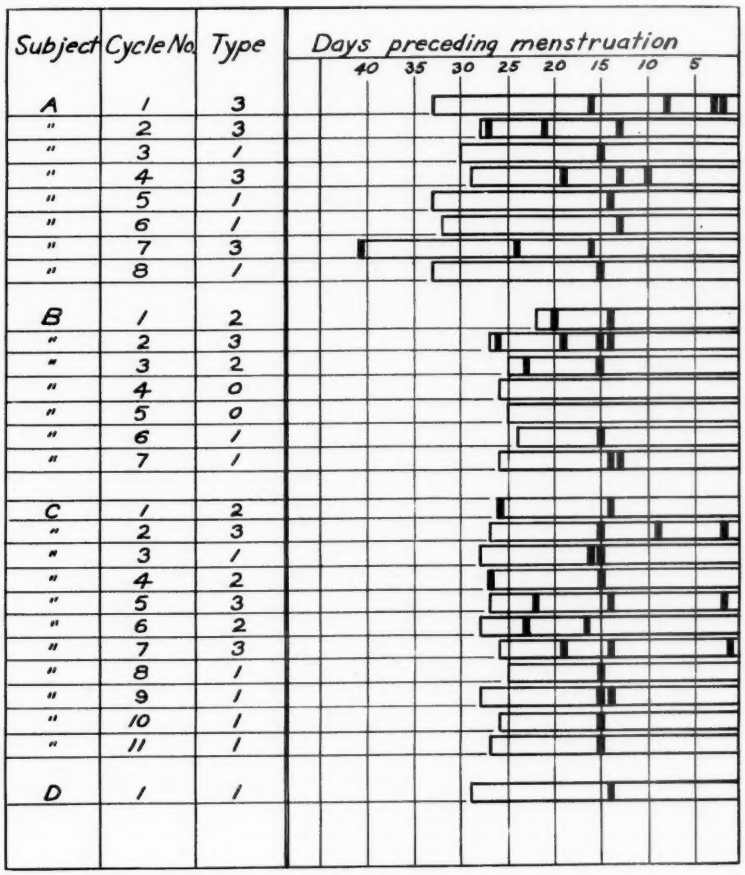

Chart 1.

Charts 1 and 2.—The blocks signify positive tests for gonadotropic substance. The different types are summarized in Table I.

TABLE I. CLASSIFICATION OF CYCLES

DESIGNATION ON GRAPH	DESCRIPTION OF CYCLE	NUMBER OCCURRING	PER CENT OF TOTAL
0	No positives at all	3	6
1	One positive, falling between days 16 to 13	21	42
1 a	One positive, falling on day 19 or 20	2	4
2	Two positives, with 6 to 12 days' interval between	13	26
2 a	Two positives, very close together	2	4
3	Three positives, at fairly regular intervals	9	18

cycles. These women were for the most part university students and their faithful cooperation in saving twenty-four-hour urine specimens (a decidedly inconvenient and occasionally embarrassing task) is greatly appreciated by the authors. A brief statement concerning each of the

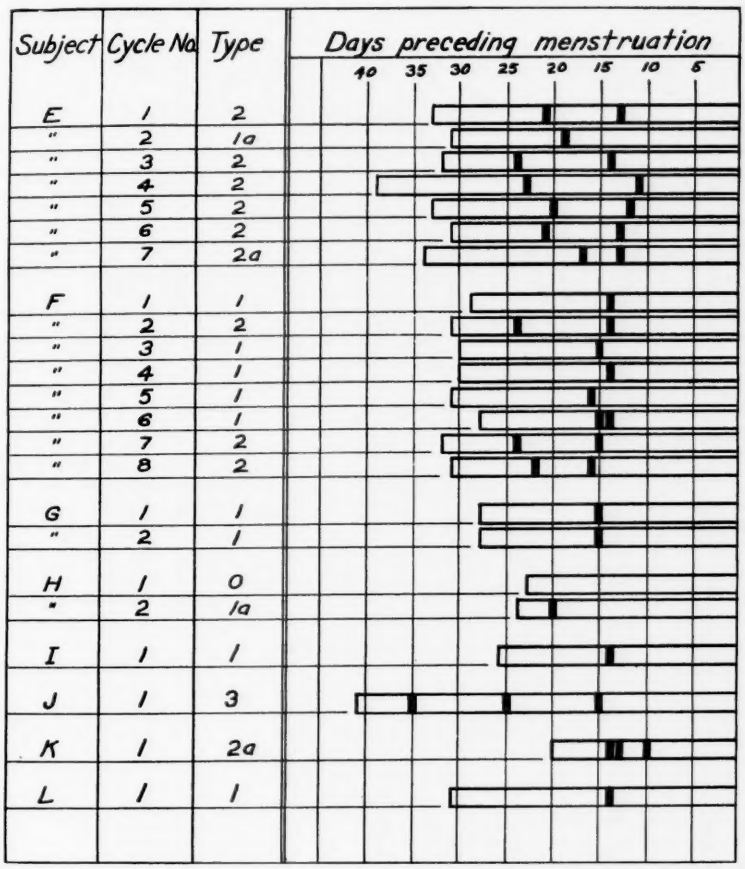

Chart 2.

subjects studied over long periods follows; the ages of the other subjects varied from 19 to 30, all were single with normal gynecologic histories.

Subject A. Aged 25, single, gynecologic history normal.
Subject B. Aged 36, single. Menses painful and protracted, condition later diagnosed as endometriosis.
Subject C. Aged 39, married, mother of three, gynecologic history normal.
Subject E. Aged 20, single, gynecologic history normal.
Subject F. Aged 20, single, gynecologic history normal.

It is at once apparent that positive reactions appear with far greater frequency than would be expected and that no type of cycle can be considered characteristic for a given subject. The classification into types is made only for the purpose of summarizing the results obtained in this study. The number of cycles, in view of the great variation shown, is

not nearly large enough to justify the conclusion that all cycles would fall into these groups nor that these percentages would hold for all women.

Histologic Results.—As stated, most of the positively reacting ovaries were studied microscopically. Again, larger numbers of animals should have been used in order to take into account individual differences among animals. This, for the reasons mentioned, was impossible. In general, it can be said that this substance is primarily follicle stimulating in its effect, however, varying degrees of luteinization had occurred in the heavier ovaries. No great difference in this respect could be noted between the positives found during the midinterval and those occurring at other times. Thus, so far as the effect produced on the rat ovary is concerned, there is no qualitative difference in the hormone produced at different times during the menstrual cycle.

Nature of the Gonadotropic Substance.—Comparative studies have been carried out on the gonadotropic substance contained in normal urine, prolan (from pregnancy urine), the gonadotropic substance in menopause urine and anterior lobe extracts. These results will be published elsewhere but may be summarized here. So far as its action upon increase in weight of ovaries and corpus luteum formation is concerned as well as its action upon the testes and seminal vesicles of immature males, the substance in normal urine seems closely related to, if not identical with, that present in menopause urine. The latter is believed by many investigators (Van Dyke,[8] pages 228 and 229) to be the true follicle-stimulating hormone of the anterior pituitary, with which belief our studies are in agreement.

DISCUSSION

The most important question in connection with this study is whether the sudden appearance of a high concentration of a substance which is capable of stimulating ovarian development in immature rodents signifies that ovulation in the human producing it is either impending or has occurred. It must be admitted at once that no such proof exists. However, the same doubt must prevail as to all indirect methods. Even inspection of the ovaries at laparotomy does not yield absolutely definite information. In fact, Hartman,[1] questions whether any observer is qualified to judge the age of a ripening follicle accurately enough to predict when it will rupture or to state with assurance how old a corpus luteum may be and thence deduce when ovulation had occurred. Of indirect methods whose use is practical over extended periods, the assay of the urine for gonadotropic substance seems to us the one which gives information most in harmony with present views concerning the control of ovulation. If any one view concerning ovarian control may be said to have gained universal acceptance it is the belief that this function is under hypophyseal control. There is no good evidence for species differences in respect to hypophyseal hormones, in other words, a substance which stimulates the ovaries of the immature rat would, presumably at least, stimulate the human ovary. Further, so far as our studies go, the urinary product possesses properties similar to, if not identical with, those of the anterior pituitary hormone itself, and, again presumably, may be considered as originating there.

On the assumption that the sudden appearance of a high concentration of gonadotropic substance in the urine indicates ovulation, examination of the data indicates that this occurred once during the cycle in 23 cases (46 per cent); twice in 15 cycles (30 per cent); three times in 9

cycles (18 per cent); and not at all in 3 cycles (6 per cent). These last may be interpreted as representing anovulatory cycles, the existence of which, in the monkey, is certain, and in the human being probable.

There are reasons for believing that ovulation may occur more than once per cycle. Of perhaps least importance, but not to be completely disregarded, is the frequent failure of conscientious effort on the part of intelligent women to control conception by means of the so-called safe period technique. Many of these failures may be due to errors in calculation, resulting from irregularities in the length of the menstrual cycle, but others may well be due to extraovulations.

A paper has recently appeared by Samuels[9] in which the time of ovulation was determined by means of the cycloscope. (This is a device which permits determination of the time of oxyhemoglobin reduction spectroscopically.) The author concludes that mature women always ovulate twice per cycle, young women three times. Here, as in all cases of indirect determination, doubt must exist as to the certainty of relation between the observed phenomenon and ovulation. However, Samuels has in some cases verified the result obtained spectroscopically by examination at laparotomy.

Certain other studies are suggestive in this connection. Gustavson and others[10] have reported on the excretion of estrin during the menstrual cycle. In this study we found that estrin excretion occurred typically in two peaks, the first being considered as related to follicular maturation and the second as due to corpus luteum activity. These peaks might be explained on a different basis, namely as two successive follicular maturations (perhaps in both cases followed by ovulation) during the same menstrual cycle. We are at present investigating this relationship by assaying the same urines for both the gonadotropic principle and for estrin.

A final point may be made for the case of multiple ovulation on the basis of the data presented. If one includes days 16 to 13 as representing the midinterval, 41 of our cycles (82 per cent) show a positive reaction at that time. If one broadens the midinterval to include days 20 to 11, 47 cycles (94 per cent) are positive. If one includes only the positive cycles, the incidence is 100 per cent. This conforms with the evidence from other sources and strengthens the view that the positive response indicates ovulation. But if that be true, one is almost forced to assume that positive reactions at other times indicate the same thing. As was pointed out previously, the response at other times was just as strong quantitatively, as indicated by ovarian weights, and of the same nature qualitatively, as indicated by histologic study, as that obtained during the midinterval. The explanation may be, though this is speculation, that the ovarian cycle and hypophyseal cycle are independent, and the gonadotropic hormone will only produce ovulation if the ovary is in proper phase with it.

As concerns the use of such a test as this in the diagnosis of sterility of hypophyseal origin, one is perhaps on safer ground. Barring the complication of an occasional anovulatory cycle in the normal female, if day by day tests over a period of several cycles were consistently negative the diagnosis of sterility due to failure of the hypophysis to stimulate the ovary would be justified. This would indicate as well that the treatment should consist of gonadotropic rather than estrogenic hormones. However, prolan would certainly not be indicated, as the effect desired is a follicle-stimulating, not a luteinizing, one. Until potent

gland extracts are available, efforts to prepare a potent gonadotropic preparation from menopause urine (or pregnant mare serum) would be worth while, as these substances appear to have the same properties as the gonadotropic substance produced by the normal female during the menstrual cycle.

SUMMARY

1. Day by day tests of the urine for gonadotropic hormone were made during 50 complete menstrual cycles. The tannic acid precipitation method was used. Positive responses were found as follows: (a) During 3 cycles, no positive response. (b) During 21 cycles, one positive response, falling between days 16 to 13. (c) During 2 cycles, one positive response, falling on day 19 or 20. (d) During 13 cycles, two positive responses, with a 6- to 12-day interval between. (e) During 2 cycles, two responses, falling very close together. (f) During 9 cycles, three responses at fairly regular intervals.

2. The bearing of these findings upon the question of the time of ovulation is discussed. The only conclusion that can be drawn is that either ovulation frequently occurs more than once during the menstrual cycle or else that ovulation is not directly dependent upon hypophyseal stimulation. In either case, the reproductive cycle in the human female is apparently a more complex and variable phenomenon than is usually supposed.

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Latzka, A.: A Positive Aschheim-Zondek Reaction in Tuberculous Disease of Uterine Tubes, Zentralbl. f. Gynäk. **61:** 277, 1937.

The writer discusses various conditions other than pregnancy that cause increase of gonadotropic output in the urine. Among others he mentions tuberculous disease of the uterine tube referring to an observation reported by Wilson. Latzka corroborates Wilson's finding by describing two personal observations. He mentions a case of threatening abortion as result of tubal adhesion. A positive Aschheim-Zondek case readily leads to the incorrect diagnosis of extrauterine pregnancy, definite differentiation being possible only by means of a laparotomy.

J. P. Greenhill.

THE ETIOLOGY AND TREATMENT OF ENDOCERVICITIS AND CERVICAL EROSIONS*

ANTHONY WOLLNER, M.D., F.A.C.S., NEW YORK, N. Y.
(From the Gynecological Department of the New York Post-Graduate Hospital)

ENDOCERVICITIS is not a sharply defined clinical or histologic entity. An excessive amount of cervical discharge, with or without erosion, is clinically regarded as evidence of endocervicitis, but since the normal cervical mucosa contains mucus-secreting glands, a certain amount of discharge is physiologic, and it is difficult to draw a dividing line between a normal and a pathologic amount of secretion. A definite diagnosis is possible in those cases in which the cervical discharge is associated with a reddened area around the external os, the so-called erosion. It is generally believed that an erosion does not exist without endocervicitis, from which it originates. Histologically, the diagnosis of a simple endocervicitis without erosion is based on the presence of hyperplasia and hypersecretion of the glandular elements. In many cases inflammatory changes in the stroma are inconspicuous or entirely absent, the prominent microscopic feature being the preponderance and hyperactivity of the columnar cells. Marked mitotic activity, with crowding and desquamation of the columnar cells, is considered as the manifestations of an inflammatory process. The histogenesis of erosions has long been the subject of controversy and a voluminous literature is available on this subject. Erosion, histologically, is not what the term implies, the protective epithelium not being really lost. The red area, which resembles a denuded surface, is covered with a single layer of columnar epithelium. By what mechanism the squamous epithelium of the portio disappears, to be replaced by columnar cells, is unknown. The generally accepted view is that the irritating hypersecretion macerates the squamous epithelium, which results in a denudation around the external os. This denudation exists for only a short time, the columnar epithelium of the endocervix proliferating rapidly over the raw area. It has been contended that this alteration is due to the fact that columnar epithelium is more resistant to maceration than is squamous epithelium. Infection is regarded as the causative factor behind these histologic changes. The invasion of the cervical glands by bacteria produces hyperemia, which eventually leads to hyperplasia and hypersecretion.

The histologic interpretation of endocervicitis and erosion, and the etiologic deductions therefrom, are based on the assumption that the cervical mucosa maintains a constant histologic structure, in which cyclic transformations due to ovarian hormone influence do not occur. In previous papers I have reported my observations, which demonstrated menstrual cyclical changes in the cervical mucosa and their correlation

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with ovarian hormonal activity. I also pointed out that various phases of the histologic cycle of the endocervix may be erroneously interpreted as inflammatory reaction. It is evident that the etiologic and histologic conceptions of endocervicitis and erosion were formulated on a basis which my previous studies seemingly controverted. The hormonal influence on the cervical mucosa is such an important factor in this structure's physiologic activity that a proper evaluation of the histologic findings does not seem possible without a knowledge and full appreciation of the effects of the ovarian hormones. If this premise is correct, it would seem logical to predict a revision of some of the previously held views concerning cervical erosion and endocervicitis.

To demonstrate the influence of the ovarian hormones on the cellular structure of the endocervix, I have carried out some experimental studies on six women whose cervical mucosa was subjected to the atrophic changes incidental to castration or the physiologic menopause.

Of the 6 patients selected, 3 were castrated surgically because of bilateral tubo-ovarian disease, and 3 were undergoing a natural menopause. These 6 women were divided into 3 pairs. Those in Group I were given estrin exclusively, in Group II progestin only, and those in Group III were treated with both estrin and progestin. In each instance a cervical biopsy was taken before beginning hormonal treatment, and the histologic picture was similar in all 6 cases. The stroma as well as the glandular structure undergoes characteristic changes after the cessation of menstruation. The stroma becomes dense connective tissue, and the cells are small, pyknotic. The blood vessels have unusually thick muscular walls. The glands are regular in outline, round or oval shaped, with collapsed lumina. The lining epithelium in some of the glands is completely cast off, whereas in others the columnar cell lining reveals signs of pyknosis. Inactivity and gradual disappearance of the columnar cell elements are the outstanding features of the menopausal cervical mucosa. I observed that after surgical castration these atrophic changes progress rapidly, whereas in the physiologic menopause this alteration is more gradual. This seems to indicate that ovarian hormone production may continue for a long time after the clinical onset of the menopause.

Another cervical specimen was taken after the completion of the hormonal treatment, and the two specimens in each case were subjected to a painstaking comparative histologic study. The history and photomicrographs of one case in each group are detailed herewith.

CASE 1.—A 41-year-old woman, married nineteen years, had one miscarriage twelve years previously, but no other pregnancies. Menstrual history normal. She presented herself complaining of a profuse yellowish bloody discharge of two weeks' duration, with severe abdominal pain in the left lower quadrant, backache, and frequent, painful urination. Gynecologic examination revealed a profuse discharge from the cervical canal, tinged with blood. The portio appeared normal. The corpus was enlarged, firm, and in good position. On the left side a large, tender tubo-ovarian mass which extended back to the cul-de-sac was palpable. The right adnexa could not be felt. The diagnosis of a left tubo-ovarian abscess was made. Operative findings confirmed the diagnosis, with the addition of diseased adnexa on the right side. A bilateral salpingo-oophorectomy was done with conservation of the uterus, and the patient made an uneventful recovery.

Eight weeks after the operation, examination of the patient revealed a small, atrophic portio, complete lack of discharge, a small uterine corpus, and a free pelvis. Before the institution of hormonal treatment a cervical biopsy was taken, the histologic study of which revealed the following: The surface was covered with a single layer of columnar epithelium with pyknotic, deeply stained nuclei. Some of the glands, which were oval or round in shape, had regular outlines and were lined with columnar epithelium similar to that found on the surface. These glands had collapsed lumina and did not reveal any signs of secretion. In the majority of the glands an extensive desquamation of the lining membranes was noted. The stroma

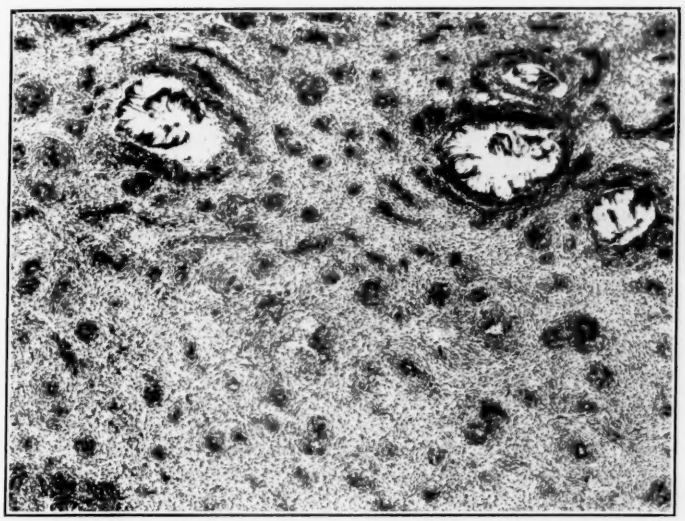

Fig. 1.—Atrophic cervical mucosa in Case 1.

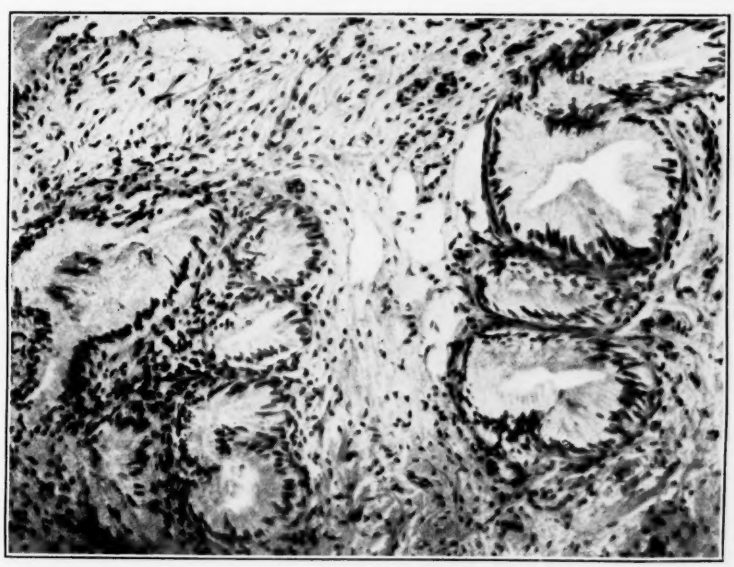

Fig. 2.—Cervical mucosa in Case 1 after the administration of 48,000 rat units of progynon B.

was a dense connective tissue with a conspicuous number of thick-walled, contracted blood vessels. Fig. 1 illustrates a typical area of this specimen under low power.

The patient received hormonal treatment over a period of six weeks. All together 48,000 rat units of progynon B were given intramuscularly. After the last injection another cervical specimen was obtained, which revealed the following picture: The surface of the mucosa showed extensive folding, imitating papillae. The epithelium was of a high columnar type; the nuclei were pale and swollen, migrating toward the center of the cells. A conspicuous number of mitoses could be seen. The glands were numerically increased, and markedly distended and branched. The lining epithelium of the glands was high columnar, with increased cytoplasm, which narrowed the glandular lumina. The nuclei were pale, approaching the center of the cells and leaving in many places a lucid zone between them and the basis. The stroma cells had swollen nuclei, and the connective tissue fibers were separated by marked edema. The blood vessels were distended by erythrocytes and a few white cells (Fig. 2).

This case demonstrates the change of an atrophic cervical mucosa into a highly active structure following the administration of large doses of estrin. In some places the typical, picture of a glandular hyperplasia was produced, similar to that found in cases of endocervicitis. The structure of the glands resembled the one usually found in the late proliferative menstrual phase. The histologic transformation of a dense, ischemic connective tissue into an edematous and hyperemic structure simulates an inflammatory condition. In the course of the treatment changes were noted in the gross appearance of the cervix. The small, firm anemic and dry portio gradually changed into a larger, soft, pink-colored structure. After the administration of 10,000 R.U. of progynon B, a scant discharge appeared from the cervical canal, which was noticeable throughout the period of treatment.

The other case in this group was that of a woman who was surgically castrated for bilateral cystic disease of the ovaries. The first cervical specimen taken ten weeks after the operation showed an identical histologic picture as in the first specimen in the case just described. This patient was given 15,000 R.U. of progynon B by intramuscular injections over a period of three weeks. The cervical specimen taken after the completion of the treatment revealed a moderate increase in the number of the glands. The glands were of irregular outline, profusely branched, and the lining epithelium was of a high columnar type, with pale, spindle-shaped nuclei. Changes in the stroma were inconspicuous. Notwithstanding the relatively small dose of estrin, a reactivation of the atrophic cervical mucosa was evident in this case.

Two patients of the second group were treated exclusively with progestin, and one case is described in detail.

CASE 2.—A fifty-seven-year-old woman, had two children thirty-five and thirty-four years previously. Seventeen years before, she had a right salpingo-oophorectomy for ectopic pregnancy. The menopause had been established ten years ago. Gynecologic examination revealed a small atrophic cervix, free from discharge, a small freely movable corpus, and the adnexa were not palpable. A cervical specimen was taken which showed the following histologic picture: The covering epithelium was partly low columnar, partly cuboidal, with deeply stained small nuclei arranged near the base. The glands were few with narrow, collapsed lumina; some were lined with low columnar epithelia, the nuclei being markedly pyknotic and basally arranged, while other glands revealed the lining epithelium in the process of desquamation. The stroma was dense connective tissue, the cells having small deeply stained nuclei. The blood vessels were contracted and had thick muscular walls. A squamous epithelial covering could be seen over a small area, showing several layers, chiefly consisting of prickle cells, and gradually decreasing to a thin layer (Fig. 3).

This patient received 60 mg. of proluton by intramuscular injections over a period of four weeks. No clinical change in the appearance of the portio was noted. After the last injection of proluton another cervical specimen was obtained and histologically examined. The glandular elements and the stroma showed a substantially identical picture with that found in the first specimen, but a marked change was noted in the histologic appearance of the squamous epithelium. An active proliferation was conspicuous, the squamous cells invading the cervical canal.

Approximately three-fourths of the length of the canal was covered with a high layer of noncornifying stratified epithelium, with complete disappearance of the columnar type. Numerous mitotic figures could be seen in the squamous epithelial layer. Fig. 4 visualizes the epithelial covering of the mucosa within the cervical canal.

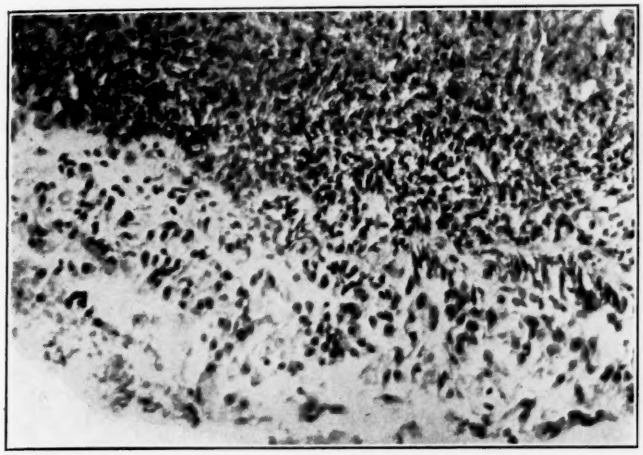

Fig. 3.—Atrophic squamous epithelium in Case 2.

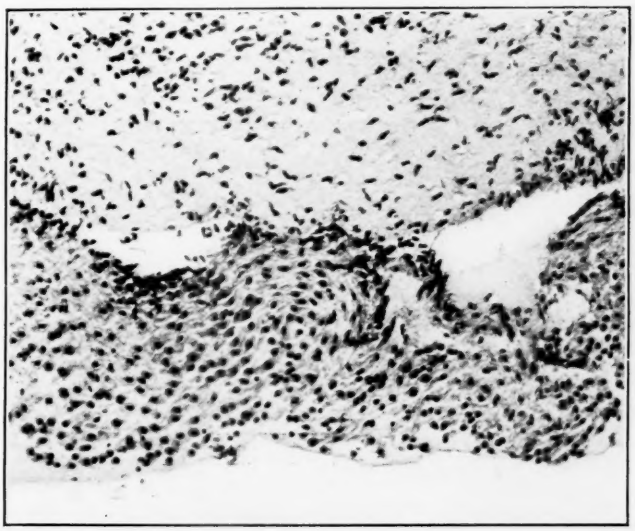

Fig. 4.—Squamous epithelium in Case 2 after the administration of proluton.

This case, in which a woman in the menopause was treated with progestin, does not reveal any appreciable histologic changes in the glandular structure or the stroma of the atrophic cervical mucosa. A marked stimulation of the squamous epithelial elements was effected, however, with resulting invasion of the endocervical surface.

In the third group, consisting of two menopausal patients, large doses of estrin and progestin were administered simultaneously. The following case report and photomicrographs demonstrate the results obtained.

CASE 3.—A 52-year-old woman, never pregnant, had always menstruated regularly until five years ago, when the menopause occurred. Gynecologic examination revealed small, atrophic genital organs. The patient complained of menopausal symptoms. A cervical specimen was taken, which showed the following picture: The surface was covered with low columnar epithelium, having little cytoplasm and deeply stained pyknotic nuclei arranged near the base. The glands were relatively numerous, but were small and symmetrically round. The lining epithelium was low columnar in some places, in others cuboidal with very little cytoplasm and deeply

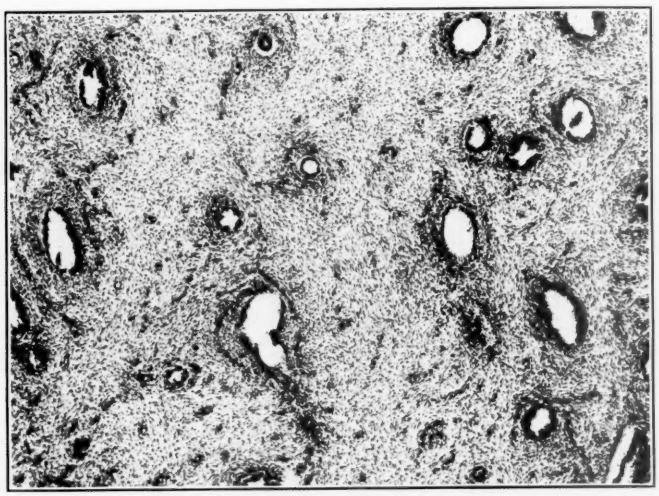

Fig. 5.—Atrophic cervical mucosa in Case 3.

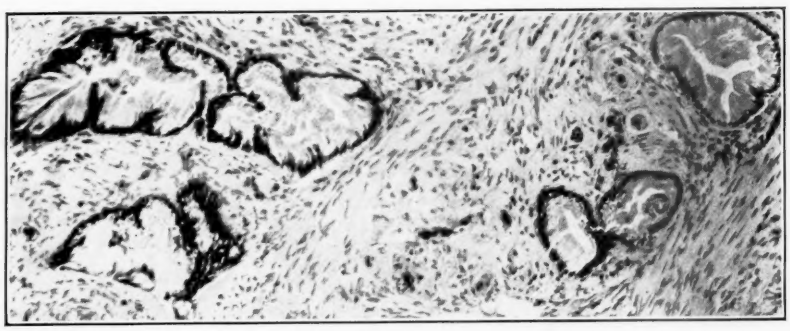

Fig. 6.—Cervical mucosa in Case 3 after simultaneous administration of progynon B and proluton.

stained small nuclei. In many glands the lining epithelium was completely or partially desquamated. The stroma was dense connective tissue, the blood vessels were contracted and had thick muscular walls. Squamous cells could not be found in any part of this specimen (Fig. 5).

The patient was treated with ovarian hormones over a period of four weeks. She received 50,000 rat units of progynon B and 35 mg. of proluton intramuscularly, and began to menstruate after the completion of this treatment, having a normal flow for five days. The cervical specimen obtained after the last hormonal injection was subjected to careful study and revealed the following: The glands were not noticeably increased in number, but revealed marked structural changes. Their shapes were irregular, with numerous projections into the surround-

ing stroma. The lining epithelia were of the high columnar type with pseudo-projections into the lumina. The nuclei were elongated, pale, and the cytoplasm was increased. The stroma had a loose texture; a few capillaries and some scattered round cells were seen (Fig. 6). An area of the surface was found to be covered with a very high layer of stratified epithelium. The basal layer of this epithelium showed irregular projections into the underlying stroma. The cells in the upper

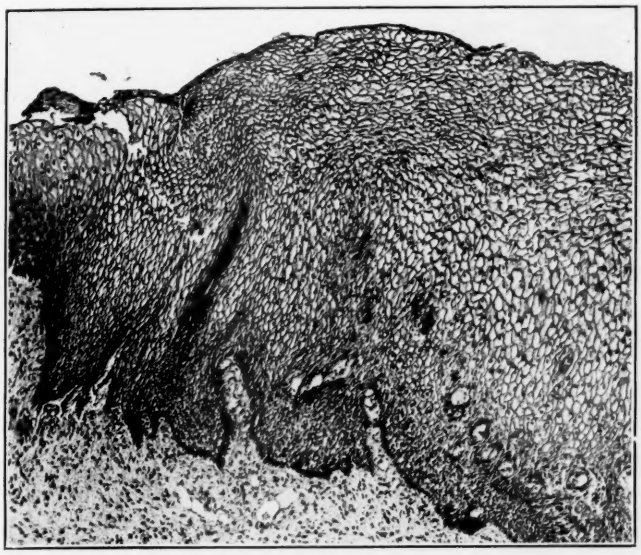

Fig. 7.—Marked hyperplasia of the squamous epithelium in Case 3 after administration of progynon B and proluton.

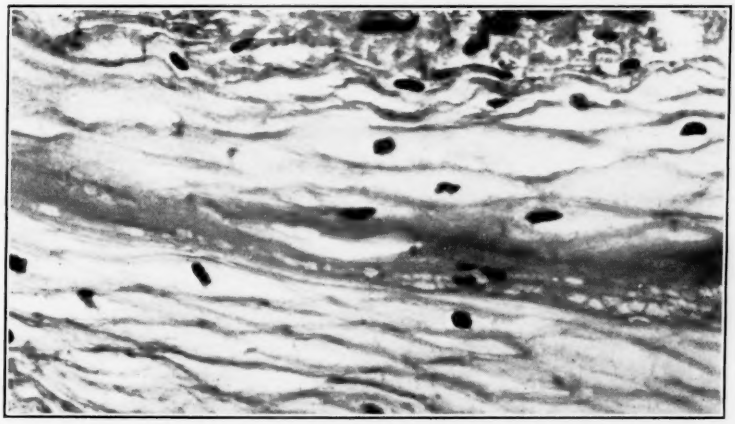

Fig. 8.—Parakeratosis in Case 3.

layers revealed vacuolization. In one small area, approximately 1 mm. below the basal layer, an epithelial island could be seen in the stroma, which was well demarcated and contained deeply stained regular epithelial cells. Fig. 7 illustrates the squamous epithelial picture in this case. A portion of the squamous epithelium revealed the typical picture of parakeratosis (Fig. 8).

The simultaneous administration of estrin and progestin produced in this menopausal patient a distinctly different histologic picture in the cervical mucosa from

that observed in similar cases treated exclusively with estrin or progestin alone. The reactivation of the atrophic cervical mucosa was as striking in this instance as in the other cases, but it seems that the simultaneous action of estrin and progestin altered the respective histologic effects of these two hormones. Notwithstanding the same dosage of estrin as in Case 1, the glandular hyperplasia and the hyperemia and edema of the stroma failed to develop. The proliferative activity of the columnar cell elements seemed to be depressed, probably due to the inhibitory influence of progestin. The squamous epithelial changes in this case deserve special comment. The marked hyperplasia resembles the embryonic type of epithelium. The histologic significance of this, and that of parakeratosis, found in another portion of the specimen, is not definitely known. Parakeratosis is an incomplete cornification of the epithelium. Schiller devoted careful attention to this condition, and believes that the portio-epithelium always possesses a latent potency for prosoplastic cornification. The stimulus which awakens this latency may be external, such as pressure, dryness, or chronic inflammation and syphilis. There are cases, however, in which para- and hyperkeratosis develop without any known external or internal stimuli, which are the spontaneous types. My observation in this case seems to indicate that prosoplastic changes of the portio-epithelium may be produced by a dysfunction of the ovarian hormones.

Summing up my observations in 6 cases, in which the histologic effects of the ovarian hormones were studied on the atrophic cervical mucosa, the following conclusions seem justified. Constant changes occurred which prove the ovarian hormonal participation in the histologic transformations of the cervical mucosa. Alterations resembling inflammatory conditions were produced by the administration of hormones. Specifically, estrin seems to stimulate the proliferation of the columnar cell elements, with hyperemic and edematous changes in the stroma. The administration of large doses of estrin changed the atrophic cervical mucosa into a structure which showed the typical picture of glandular hyperplasia with marked hyperemia, a condition commonly found in endocervicitis cases. Progestin, on the other hand, seemed to stimulate the growth of the squamous epithelial elements. The invasion of the endocervical surface by this epithelium was pronounced after the administration of progestin. There is suggestive evidence that the combined action of estrin and progestin alters the specific histologic effects of the individual hormones. Progestin seems to exert a certain inhibitory effect on the estrin action, while estrin seems to accentuate the progestin's stimulating effect on the squamous epithelium.

Endocervicitis and erosion are chiefly characterized by an active proliferation of the columnar epithelium, deep in the stroma in the form of a glandular hyperplasia, and on the surface by considerable folding of the covering columnar layer and invasion of the portio surface. According to my observations such histologic changes may be produced by an unopposed estrin action. Should this etiologic consideration be true, the inhibitory effect of the progestin may be used for practical purposes, in bringing about a control of the pathologically active estrin function. To ascertain whether histologic pictures in the cervical mucosa, regarded as endocervicitis, can be influenced by the administration of progestin, further studies were carried out. Three nulliparous patients between the ages of 25 and 34 were selected. They all had a profuse cervical discharge with marked erosions, but otherwise were normal. Cervical specimens were taken from all three and showed

identical histologic pictures. Treatment with progestin was begun and continued for two months in each case. After completion of the treatment another cervical specimen was taken on exactly the same day of the intermenstrual period as the first one. The two specimens in each case were subjected to a comparative study, with the same results in all three cases. The following case and photomicrographs are typical.

CASE 4.—A 31-year-old woman, married for eight years, never pregnant. Menstruates profusely every twenty-six or twenty-eight days, lasting seven to eight days. Patient's chief complaints were: Menorrhagia and profuse white discharge. There was a marked erosion around the external os, with a profuse yellowish discharge from the cervical canal. The uterus was slightly enlarged, firm, freely movable, and the adnexa were negative. The first cervical specimen was obtained on the sixteenth day after the day of onset of her previous menstruation. Histologic study revealed the following: The surface was covered with high columnar epithelium. The

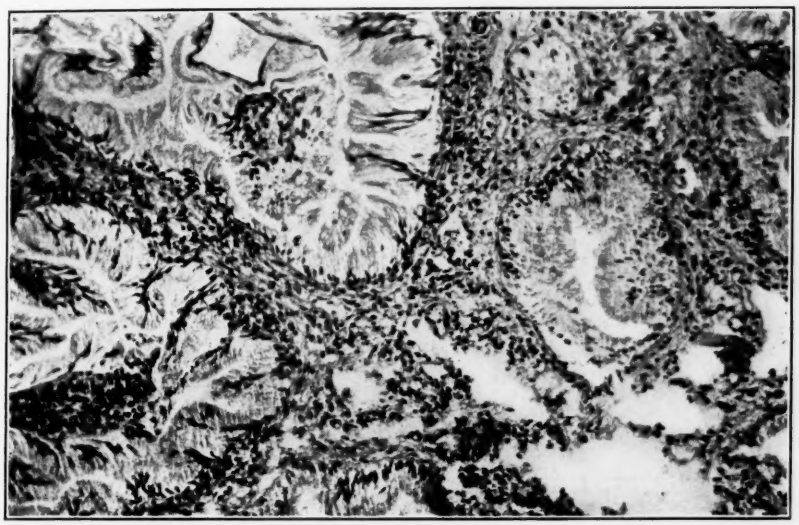

Fig. 9.—Glandular hyperplasia in Case 4.

nuclei were near the basal membrane and were deeply stained. The glands were closely packed, with papillary projections into the lumen due to the folding of the lining epithelium. The columnar epithelial lining of the glands consisted of very high cells with much cytoplasm; the nuclei were relatively small, situated near the basal membrane; many cells were markedly swollen and among these some were of the basket cell type. The stroma was markedly edematous, a few arterioles had their lumina filled with erythrocytes and a few white cells. Fig. 9 represents this specimen, showing the characteristic picture of a glandular hyperplasia in the early secretory phase.

The patient received in all 45 mg. of proluton by intramuscular injections over a period of two months. Its clinical effect was a change in the menstrual bleeding. While menstruation appeared at the expected time, the first period after beginning treatment was only of five days' duration with a moderate flow, and the second one thereafter lasted only four days with scanty bleeding. The usual symptoms of discomfort during the first two days of menstruation were entirely absent. After the proluton therapy a second cervical specimen was taken again on the sixteenth day following the first day of the bleeding. The histologic picture of this specimen shows the surface covered with partially low, partially cuboidal columnar epithelium.

The swollen nuclei are pale everywhere and do not reach the basal membrane. Few of them reveal migration toward the center of the cells, showing in such places a lucid zone between them and the basis. Indications of secretion are conspicuously absent. The stroma is dense and contains a few thick-walled arterioles and capillaries. These characteristics represent the proliferative phase of the menstrual cycle. Fig. 10 is a low power visualization of this picture.

In three cases of endocervicitis and erosion the administration of progestin produced marked histologic changes in the cervical mucosa. In all three a moderate decrease in the number of glands was noted, the hyperemic and edematous stroma changed into a dense structure, and apparently the persistent progestin action disturbed the normal course

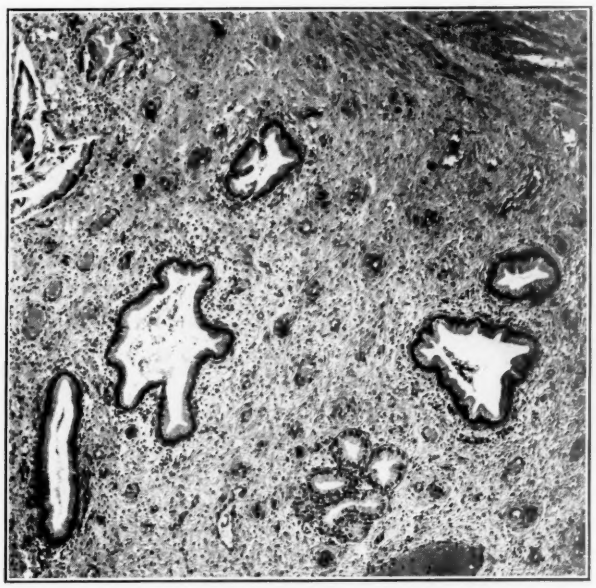

Fig. 10.—Cervical mucosa in Case 4 after the administration of proluton.

of the histologic cycle, since the secretory phase failed to develop at the expected time, the glands remaining in the proliferative stage. For the proper evaluation of these results it must be remembered that proluton was not given for therapeutic purposes. Small doses over a comparatively short period of time were administered only to ascertain whether the hormonal principles in the histologic interpretations of the cervical mucosa could be corroborated. Had infection been the etiologic factor in these cases, treatment with progestin would not have changed an inflammatory histologic picture in the cervical mucosa. The progestin effect in these cases not only proves indirectly that overproduction of estrin was responsible for the changes usually regarded as endocervicitis, but also intimates that the therapeutic problems involved in this condition may be approached on a hormonal basis.

DISCUSSION

Endocervicitis and erosion are generally believed to be the results of an inflammatory process due to infection. However, in the majority of

cases a specific infectious agent cannot be ascertained by clinical investigation. Furthermore, it is a recognized fact that the present histopathogenetic explanation of erosions cannot be verified by the histologic findings in many cases. The physiologic function of the two cervical epithelia, and its dependence on ovarian hormonal activity not having been recognized, histologic interpretations in the cervical mucosa have been made on a theoretical basis. According to my observations, ovarian hormone action is capable of producing histologic changes in the cervical mucosa, which have formerly been interpreted as inflammatory conditions. The possibility of a hormonal-cervical pathologic alteration makes the infectious-inflammatory etiology of endocervicitis and erosion problematical. In an attempt to determine the histogenesis of this pathology, the clinical and histologic manifestations of endocervicitis and erosion must be subjected to a critical survey.

The clinical occurrence of endocervicitis and erosion is not limited to any age-group, from the time of birth to the age of menopause.

Fischel investigated the portio of twenty-eight stillborn female infants, and found cervical erosion in 36 per cent of his cases. R. Meyer places the incidence of erosions in newborn infants at 33 per cent. No statistical data are available on the prevalence of erosions in young virgins, the inspection of the portio through an intact hymen not being practicable. Excessive cervical discharge in young girls, however, is not rare and observations in occasional cases, in which speculum examination can be carried out, indicate that clinical symptoms of endocervicitis and erosion are as frequent in this age group as they are in adults. Fulkerson studied 6,483 adult women and found an incidence of 33 per cent of endocervicitis.

After the menopause and after surgical removal of the ovaries, the incidence of this pathologic condition is distinctly less. The occurrence of endocervicitis and erosion in a fairly constant percentage from the time of birth to the age of menopause, and its disappearance after the cessation of ovarian activity do not seem to support the theory of an infectious etiology; on the contrary, it is suggestive of an interrelationship between hormonal action and the pathology.

Bacterial invasion of the cervical glands with resulting hyperemia and hypersecretion is supposed to be the cause of endocervicitis and erosion. Several investigators (Stroganoff, Menge, Curtis, etc.) have reported that bacteria are not normally found above the level of the external os. It remains problematical whether or not bacteria are able to pass through the external os, unless a predisposing hormonal factor is present. The most frequent source of female genital infection is the gonococcus. This specific agent is believed to play a prominent role in the production of endocervicitis. Kidd and Simpson investigated 223 cases of known gonorrheal infections and found erosions in 20 per cent of them. In 382 cases in which gonorrhea could be ruled out, erosions were found in 40 per cent. Consequently, erosion was found to be twice as frequent in nongonorrheal as in gonorrheal patients. This observation seems to prove that there is no causative correlationship between gonorrhea and erosion. Another possible source of female genital infection is incidental to labor. Traumatism of the cervix

during labor is presumed to facilitate invasion by bacteria, with subsequent inflammatory changes. This theory seems to be supported by the clinical observation that erosion is more frequently found in parous than in nonparous women. According to the estimation of various authors, the incidence of erosions is 80 per cent in parous as against 25 per cent in nulliparous women. These statistics imply that 55 per cent of all women who undergo labor are exposed to infection, with resulting permanent damage to the cervical structure. In the proper interpretation of these figures certain factors have to be taken into consideration. The fact is that a considerable number of women have their first gynecologic examination after childbirth. When evidences of endocervicitis and erosion are found at this time, there is a tendency to attribute them to birth trauma, although the condition may have been present for a long time before confinement. It may have passed unrecognized, since this pathology does not necessarily produce symptoms which would make a gynecologic consultation imperative. The establishment of a causal relationship between childbirth and erosion would be possible only if cervices were to be regularly inspected before and after confinement. Such a scrutiny of patients is rarely undertaken. Another important factor is the observation that erosion frequently makes its first appearance during the course of pregnancy. These so-called pregnancy erosions are rarely recognized, since speculum examination of pregnant women is not routinely made. Such erosions are definitely of noninfectious origin and may persist long after the confinement. Etiologically, their association with hyperfolliculinism of the ovaries, concomitant with pregnancy, is a reasonable hypothesis.

The clinical course of endocervicitis and erosion is unparalleled by any other inflammatory process in the genital tract, as these lesions are known to persist for many years, without any tendency toward spontaneous cure. Furthermore, they are highly resistant to the usual treatment of inflammatory conditions. In the course of several years, sudden exacerbations or recurrences may occur without any evidence of a new infection. The lack of recuperative power in the cervix is difficult to explain, since it is acknowledged that other parts of the genital lining membranes are capable of returning to normal within a relatively short period of time, even after profound structural changes. It has been contended that the cause of the cervical mucosa's different behavior in inflammatory processes can be explained by its unchangeable character. This theory is no longer tenable, since the histologic cycle in this structure has been demonstrated. Undoubtedly, irritative factors other than infection may account for this pathologic condition's persistency. The ever changing ovarian hormone action may account for the unstable appearance of erosions, and the failure of cure with antiseptic medications.

That erosion is not a localized process, strictly confined to the uterine cervix, is substantiated by several associated clinical symptoms. The size and consistency of the uterine corpus, as well as those of the cervix, are changed in these cases. Large uteri with hypertrophied cervices are

usually found associated with erosions, their consistency being soft, somewhat resembling an early pregnancy. The menstrual history usually discloses profuse and prolonged bleedings. Erosions do not occur in genital hypoplasias. All of these clinical manifestations are strongly suggestive of an ovarian participation in the pathology of erosion, involving to a certain degree the entire genital tract.

This short critical review of the clinical features of endocervicitis and erosion clearly demonstrates that there is no conclusive evidence to support the theory of an infectious origin, whereas an objective interpretation of the clinical symptoms strongly indicates an ovarian hormonal influence.

A scientific determination of the genesis of endocervicitis and erosion is possible only by an analytic histologic study of the cases. When the entire vaginal surface of the portio of the cervix is covered with squamous epithelium, it is considered to be normal. An extension of the columnar lining of the cervical canal to the outer surface of the portio constitutes the clinical picture of erosion. The histologic process whereby the replacement of the squamous epithelium by the columnar type is effected is not definitely known. The maceration theory assumes that the irritative action of the mucopurulent cervical discharge is responsible for the destruction of the squamous epithelium. Clinical observations prove, however, that many cases with profuse mucopurulent discharge from the cervical canal are seen without an erosion formation. It is evident, therefore, that discharge alone cannot explain the genesis of erosions. Furthermore, it is a known fact that histologically the squamous epithelium is a sturdy, resistant structure, much more so than the columnar epithelium. Nature provides squamous epithelial coverings on surfaces which are likely to be exposed to irritations. Histologic experience has shown that squamous epithelium reacts to chemical irritations not with loss of tissue, but with a protective proliferation. There is no evidence to indicate that the squamous epithelium of the portio is in any way biologically different from that found elsewhere. Considering all these facts, the active proliferation of the columnar cell elements with concomitant disappearance of the squamous epithelium cannot be explained satisfactorily on a maceration basis.

The outstanding histologic feature, uniformly found in all endocervicitis and erosion cases, is a pathologic preponderance of the columnar cell elements. Other histologic changes, such as hyperemia, edema, leucocytosis, desquamation, are present in some cases, and absent in others. I have demonstrated in previous papers and in the present experimental studies that all these histologic changes may be produced in the cervical mucosa by hormonal stimulation. Consequently, the histologic interpretation of these pictures should be made on the same basis as in the endometrium. Just as the terminology of endometritis was discarded, and replaced by hormonal dysfunction, endocervicitis should be reevaluated on a hormonal basis.

In the hormonal explanation of the histogenesis of erosions, certain developmental facts have to be considered. In the intrauterine development of the fetus the entire genital tract is primarily lined with

columnar epithelium. This type of epithelium is gradually replaced by squamous epithelium in the vagina, the transformation beginning at the sinus urogenitalis. From there the squamous epithelium begins to grow upward into the vagina, until the level of the external os is reached. According to R. Meyer, in about one-third of the newborn infants, the upward growth of the squamous epithelium is arrested before the external os is reached, and these cases show the clinical picture of erosion. In another one-third, the demarcation line between the two epithelia is at the anatomic site of the external os. In the remaining third, the squamous epithelium grows upward beyond the external os; in these cases the junction of the two epithelia is found within the cervical canal. According to these observations, only in one-third of the cases do the two epithelia meet at the anatomic designation of the external os. Although the factor governing the relationship between the two epithelia is not known, R. Meyer expressed the view that probably ovarian factors are important influences. His view was supported by noting that after birth, the fetal uterus becomes markedly decreased in size. The emancipation of the infant from the maternal ovarian influences seems to be a logical explanation of this phenomenon. The results of my recent studies leave little doubt of the nature of the influences which regulate the equilibrium of the two epithelia in the cervix. Estrin has a stimulating effect on the growth of the columnar epithelium. The increased production of this hormone in pregnancy is bound to exert its influence on the fetus through the blood circulation. The differentiation of the two epithelia in the genital tract of the fetus begins when the independent function of the fetal ovaries is established. It is fair to assume that thereafter the extent to which the squamous epithelium is able to displace the columnar epithelium in the vagina and on the portio will depend on the individual hormonal capacity of the ovaries. Since the balance between the two ovarian hormones is unstable, the two epithelia are in a constant restless stage, and consequently, the line of demarcation is not permanent. It is not justifiable, therefore, to designate any fixed line in the genital tract as normal for the junction of the two cervical epithelia. In the pathologic evaluation of cervical erosions, this fact should be considered.

Erosions, notwithstanding their identical clinical appearances, are divided into two large groups: the congenital and the true. An exact histologic criterion by which a clear-cut differentiation between these two types can be established is not available. They both have in common a single layer of columnar epithelial covering on the surface of the portio, with marked increase of the glandular elements in the stroma. There are cases in both groups which reveal a complete lack of inflammatory changes; on the other hand, several congenital erosions have been found with signs of marked hyperemia. There is no way of determining in an adult whether a certain lesion is a persistent congenital or an acquired erosion. It must be remembered that a congenital erosion is certain to undergo histologic changes after the menstrual cycle becomes established. A misinterpretation of the effects of the

histologic cycle in the cervical mucosa may be responsible for a false differentiation between the two types of erosions.

The treatment of endocervicitis and erosion is often a vexing problem. Numerous methods have been advocated for its cure, but it must be conceded that no single method of treatment is available which will produce uniformly satisfactory results. The new concept of a hormonal etiologic factor offers a new approach to the therapy of this condition. Should further investigations substantiate the results of my present study, hormonal treatment of endocervicitis may become feasible. Such a study is now in progress. It seems probable that the present unsatisfactory results in the treatment of endocervicitis and erosion are due to the fact that the underlying pathologic cause of this condition has not been recognized. A conservative local treatment of a constitutional hormonal pathologic condition cannot produce good therapeutic effects; on the other hand, the discouraging results of local treatment may induce gynecologists to perform radical operations on the cervix which are unwarranted. It is to be hoped that the further study of hormonal therapeutic measures will eventually develop a cure for endocervicitis and erosions.

I am indebted to Dr. W. H. Stoner of the Schering Corporation for having placed at my disposal the necessary supply of progynon B and proluton.

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116 East 68th Street

DISCUSSION

DR. VINCENT P. MAZZOLA.—These extensive studies demonstrate the changes which occur in the cells of the mucous membrane of the cervix, corresponding to those in the endometrium of the uterus, as shown by endometrial and cervical biopsies. An increase of cervical discharge may be caused by hyperplasia of glands as a

result of increased hormonal stimulus. Hence we should rule out the possibility of increased hormonal influence before making a diagnosis of endocervicitis. He has suggested also that the administration of one of the ovarian hormones can produce a proliferation of certain structures of the cervical mucous membrane, and the other hormone of the ovary, the corpus luteum, can produce a secretive effect and also a condition whereby these so-called erosions, which result from the over-production of columnar epithelium from increased ovarian stimulation, can be transformed into the stratified type.

DR. HARVEY B. MATTHEWS.—A certain proportion of the cervices that are supposed to be infected might come under Dr. Wollner's new etiologic classification. I believe that a certain number of these cervices, even though they are under the stimulation of hormonal secretions, are infected. A certain percentage of them (say 25 or 30 per cent) are or have as their basis an infection, perhaps superimposed on a hormonal stimulating process. But I believe the doctor has started an investigation that may lead us to change our opinions about a certain proportion of so-called cases of chronic endocervicitis with erosions.

DR. SANFORD KAMINESTER.—One question comes to mind. Dr. Wollner finds that with the administration of estrone there is a marked increase in the glandular elements whereas administration of progesterone causes an increase in the squamous cell epithelium.

Several years ago, when the use of estrone was advocated for the treatment of gonorrheal vulvovaginitis in young girls, it was shown by vaginal biopsy that the use of this preparation caused a proliferation of the surface epithelium. Can Dr. Wollner correlate the apparently opposite effect in his material with the previous work?

DR. SAMUEL A. WOLFE.—In a discussion of endocervicitis we must confine our views only to those lesions which are definitely inflammatory in nature. In the acute phase the exudate is composed almost entirely of polymorphonuclear leucocytes. In the subacute phase the lymphocyte or the plasma cell predominates. In a period of fifteen or sixteen years, all cases of erosion of the cervix which I have observed have had an inflammatory basis.

The hyperplasia of the endocervical mucosa produced by estrin is not endocervicitis, but endocervical overgrowth, which is the result of vascular congestion. Leucorrhea is not uncommon in newly wed women or virgins without evidence of infection. Smears are negative and pus cells in the discharge are scant or lacking. The cervix is filled with thick, tenacious mucus and sterility is often an associated symptom. I believe this is the group of cases which Dr. Wollner has described to us tonight. Patients who present an increased growth of glands and secretion of mucus have leucorrhea. Hyperemia from excess coitus, mechanical displacement of the uterus, and unsatisfied sexual contact produces symptoms and findings similar to those experimentally produced by estrin injection.

DR. WOLLNER (closing).—I hope I did not convey the impression that I have found a new cure for endocervicitis. I have simply reported my observations that by the administration of hormones I was able to change the histologic picture in the cervical mucosa, and I expressed the hope that eventually a hormonal cure will be found for this pathology. I do not think that by the administration of progestin alone, we may effect a cure in endocervicitis and erosion cases.

I agree fully with Dr. Matthews in what he said about infected cervices. The question is, whether normal cervices may become infected and subsequently develop the clinical picture of endocervicitis and erosion, or is a hormonal predisposition in the form of erosion the primary factor with which infection becomes associated later on.

According to my observations there is a constant cyclical change going on in the human cervical mucosa, and in certain phases of this cycle histologic pictures are found which resemble inflammatory conditions. At the present time there is a

certain confusion among pathologists as to what should be considered the normal histologic picture in the cervical mucosa.

Observations were reported by several authors which showed a marked proliferation of the vaginal squamous epithelium after the administration of estrin. It must be remembered, however, that my experiments were carried out on patients with nonfunctioning ovaries. It is a question how estrin administration influences normally functioning ovaries. In my reported Case 3, it could be observed that if estrin is given simultaneously with progestin, a marked hyperplasia of the portio-squamous epithelium was present.

HORMONE FACTORS IN THE TOXEMIAS OF PREGNANCY*

With Special Reference to Quantitative Abnormalities of Prolan and Estrogens in the Blood and Urine

Howard C. Taylor, Jr., M.D., and Eugene N. Scadron, M.D.,
New York, N. Y.

(From the Department of Obstetrics and Gynecology, New York University College of Medicine, and the Obstetrical and Gynecological Service of the Third [New York University] Surgical Division, Bellevue Hospital)

THE responsibility of the placenta for eclampsia and related diseases of pregnancy is an old theory which has been repeatedly revived in various forms. The clinical evidence has always appeared simple and straightforward, for the disease occurs only in pregnancy, and improves rapidly after delivery or the death of the fetus. Furthermore it has seemed unlikely that the fetus itself could be concerned, since cases of toxemia have occasionally been noted with hydatidiform mole. A succession of different substances originating in the placenta have been blamed as medical research has passed through periods of special interest in them. At present it is obvious that the specific hormones elaborated by the placenta—the estrogens, progesterone, and the gonadotropic substances—must be given consideration in this respect.

Although these substances are present in the blood of nonpregnant women, their concentration is greatly increased during pregnancy. It is true that figures for many other constituents of the blood show slight or moderate deviations from nonpregnant levels, but these hormones may increase a hundred or a thousand fold. They are undoubtedly responsible for much that is specific in the physiology of the pregnant woman. Since pre-eclamptic toxemia and eclampsia are diseases occurring only under the peculiar physiologic conditions of pregnancy, it can hardly be questioned that in some sense the hormones play a part in their origin.

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This is giving the question of the relation of the hormones to toxemia an affirmative answer, but one in such a broad sense that it is of little practical value. Nevertheless it is worth while to point out that the present problem is to determine not whether the placental hormones are a factor in the toxemias of pregnancy, but to what extent and in what manner.

THEORETICAL CONSIDERATIONS

To be the cause of pre-eclamptic toxemia, an agent must produce certain clinical symptoms, certain changes in the blood and urine and some characteristic pathologic lesions. Several hypotheses present themselves as to how the many manifestations of the disease may be brought about through the agency of the placental hormones.

a. *Direct Action of the Placental Hormones.*—The first possibility that these substances cause the disease directly is most improbable. The estrogens, progesterone, and prolan are normal substances and their functions are not directly concerned with the body systems apparently at fault in the late toxemias. The production of hypertension, for example, is totally beyond their known scope, nor do the liver and kidney lesions appear to be producible by them. One observation, it is true, exists to the contrary—that of Tschaikowsky,[61] who in 1932 reported degenerative changes in the kidneys, liver, lungs, and blood vessels of mice following the injection of folliculin. Since his time, however, countless mice have been injected with estrogenic and other substances during the course of studies of mammary carcinoma, and no further suggestion has been made of a toxic effect of the estrogens. In excluding the possibility of a direct action of the placental hormones, one must make the reservation that unusual forms of these substances or intermediate products of their metabolism may occur which have a direct effect, but the existence of such toxic substances is at present largely hypothetical.

b. *Intermediate Effect Through Their Influence on General Metabolic Processes.*—A second possibility is based on the observation that the placental hormones in addition to their known effects on genital development and function have secondary actions on more general physiologic processes. Various reports for instance have suggested that the estrogenic substances may raise the basal metabolism, may produce a temporary hyperglycemia by freeing and thus reducing liver glycogen[1] and may even in certain animals cause a rise in the ketone bodies in the blood.[43] More pertinent perhaps have been the recent series of observations showing that the estrogens have the property of causing a retention in the body of sodium and of water (Thorn, Nelson and Thorn[60]). The slight edema of many normal pregnancies and the greater fluid retention of toxemia are conceivably due to this property of the estrogens, made effective by the high concentrations in which they occur in pregnancy.

c. *An Intermediate Effect Through Their Influence on Other Endocrine Glands.*—Perhaps, however, if the three placental hormones are to bring about the triad of hypertension, edema, and albuminuria, they must do so indirectly through their effect on the pituitary, the adrenal, or the thyroid. That these glands may each be affected in function, as well as in structure, by the estrogens is well established. Furthermore, each of these glands has at some time been regarded as a probable factor in toxemia.

1. The posterior pituitary on account of its vasopressor and antidiuretic functions has been particularly studied. The beginning of the pituitary theory dates back at least to a theoretical paper of Hofbauer[31] in 1918. Theory was converted into a burst of animal experimentation by the observation in 1927 of substances from the blood of eclamptics which caused expansion of the melan-

ophores in frogs (Küstner and Biehle[40]) and four years later the reported discovery of pressure raising and antidiuretic substances in the blood of eclamptic patients (Anselmino and Hoffmann[2]). Repetition of Anselmino and Hoffmann's work has largely tended to discredit their results, although some confirmation has been forthcoming (Theobald;[59] Byron and Wilson;[12] Levitt;[41] Hurwitz and Bullock;[36] Page[44]). The studies of Dieckmann and Michel,[15] showing the heightened vascular and antidiuretic responses of patients with toxemia to injections of posterior pituitary extract, give some support to this gland as a factor in toxemia.

2. An anterior pituitary factor in eclampsia has been suggested on the basis of some occasionally described histological changes (Kermauner,[39] Scriba,[49] Shallock,[50] Cushing[14]) and upon the report of a great variety of supposedly anterior pituitary derivatives in the blood of pregnant and pre-eclamptic patients. These include the true gonadotropic hormone of the pituitary; thyrotropic, antithyrotropic (Wiegand[64]) and corticotropic substances (Jores;[37] Fauvet and Münzner[21]); and certain fat and carbohydrate metabolism hormones (Hofmann[32]). Many of these fabulous substances have been reported by only one observer, and little attempt has been made on the part of other workers to confirm or deny their presence.

3. The adrenal has received somewhat less attention than the pituitary. Absence of the usual pregnancy hypertrophy of the adrenal cortex (Fauvet[19]) and low values in corticotropic hormone (Fauvet and Münzner[21]) have led to the suggestion of a cortical deficiency in toxemia. Such a deficiency should, however, give a clinical setting somewhat similar to Addison's disease, very much the reverse of the usual syndrome of eclampsia. One observer (Macchiarulo[42]) has claimed a hyperadrenalinemia in eclampsia.

4. The thyroid has also been held responsible. Several studies have indicated that the usual pregnancy rise in basal metabolism fails to occur or is at least less marked in cases of pre-eclampsia (Hughes[35]). A recent hypothesis (Bartholomew and Kracke[6]; Bartholomew and Colvin[5]; Patterson, Hunt and Nicodemus[45]) has attributed to this relative hypothyroidism a series of events beginning with hypercholesterinemia and progressing through placental endarteritis to placental infarcts and eclampsia.

In now considering particularly the role played by the hormones produced in the placenta, the question at once arises as to why when all pregnant women experience a great increase in the concentration of these substances, do only certain patients react with the symptoms of toxemia? Here, assuming that these hormones do play a significant part in the disease, there are three possibilities.

a. The placental hormones in the toxemic patient may be identical with those of other women and the toxemia occur simply when the constitution is especially susceptible to the normal rise in concentration of these substances in pregnancy.

b. It is possible that these hormones are qualitatively changed in the toxemic patient. This view has been urged by Smith and Smith,[54] who have presented evidence to show that the estriol fraction of the urinary estrogens is decreased, due perhaps to a failure of conversion from estrone. They also offered the hypothesis that the disease might be produced by toxic "breakdown" products of estrogen destruction.

c. Finally, there may be not qualitative, but quantitative, changes in the concentrations of these hormones. Several reports in this country by Smith and other workers and numerous scattered observations in Germany have indicated high levels of prolan and low levels of estrin in pre-eclampsia. The apparent definiteness of the results re-

ported and the evident importance of these substances in the physiology of pregnancy give such a discovery enormous possibilities. The present report is an attempt to check further these observations and is based on the studies of the estrogens, and prolan in the blood and urine of 48 patients in the last trimester of pregnancy.

It is essential that any one who wishes to form an intelligent opinion of work in this field should have some idea of the way in which the reported figures for the estrogens and prolan of the blood and urine are obtained and of the degree of accuracy they represent. He must understand that the biologic methods of assay involve possibilities of considerable error; that the methods of different laboratories have varied too much to permit as yet the acceptance of any absolute values as characteristic even of normal pregnancy, and that finally the range of values for uncomplicated cases is evidently a wide one. Hence for any figure to be regarded as significantly abnormal, it must be compared with values worked out for normal controls by the same laboratory and must differ from these by a considerable margin.

PROLAN DETERMINATIONS

The extraction of the urine was accomplished by the familiar alcohol precipitation procedure of Zondek.[65] By this method 100 c.c. of 95 per cent alcohol were added to 20 c.c. of the twenty-four-hour urine specimen after the latter had been made acid with a few drops of glacial acetic acid. The precipitate was allowed to stand in the refrigerator over night, was centrifuged the following morning, and was then washed several times with ether to remove any contaminating estrogens and allowed to dry. The resulting powder was dissolved in normal saline, adjusted to a pH of 8.5 and brought up to the original volume. The extract was always kept in the ice box until ready for use, the centrifuging being repeated immediately before injection.

For assay of the serum hormones, 50 c.c. of blood was withdrawn and centrifuged at once to separate the cells. In the majority of the tests the serum was assayed directly without further extraction. This seemed wise in order to avoid the inevitable loss entailed by more complicated procedures. Katzman and Doisy[38] for example have shown that percentages of recovery by the various so-called precipitation methods may be as low as 50 to 80 per cent. This use of unextracted serum for prolan determination involves the possible risk of a complicating effect of the estrogens also present in the serum, since it has been shown that estrin may stimulate the test animal's own pituitary to produce luteinizing substance (Fevold and Hisaw[22]). It does not appear, however, that such a possibility can seriously affect the results. The amount of serum estrogen present in toxemias and normal cases is not very dissimilar and its presence should therefore affect all of the cases to a similar extent. Further, it has been shown by Hohlweg[34] that the rat pituitary is not susceptible to estrogen before the twenty-fifth day which, if a correct observation, excludes complicating effects in prolan assay on immature rats.

Prolan assay: Some workers, particularly in Germany, have reported figures in the study of toxemias for both prolan A and prolan B. In view, however, of the persistent uncertainty as to the distinctness of

these two substances and the difficulty of recognizing slight degrees of follicle ripening, the assays in this study were based only on corpus luteum formation.

The test animals used were immature white female rats, approximately 21 days old, and weighing from 20 to 25 gm. The individual doses were divided into five injections given over a period of two days. Ninety-six hours after the first injection the animals were sacrificed and the ovaries grossly examined. By inspection of the ovaries it was possible to determine roughly where the end point would occur. The ovaries of the group of animals just above and just below this probable end point were then serially sectioned and stained. Whenever microscopic examination of these indicated an error in gross reading, the ovaries of the next group of animals, which had been kept in formalin with this possibility in mind, were also sectioned. The final reading depended therefore upon the microscopic search of serial sections for corpora lutea. By this procedure usually not more than 10 and rarely more than 15 ovaries needed to be sectioned for each urine assay.

A few special points need to be emphasized in regard to the procedure of the test.

a. The microscopic sectioning is perhaps of considerable importance. Even after several months of reading ovaries grossly with the naked eye, frequent errors were made. With the dissecting microscope these errors were reduced, but a few mistakes still occurred. If gross readings had been depended upon alone, our average values would have been lower by perhaps a fifth which means that figures for certain individual cases might have been half their actual value.

b. The crude extracts of prolan are somewhat unstable so that the assay should be performed as soon as possible after they have been made. For this reason it is inadvisable to attempt economy by using a few animals only the first week to get a general idea of the strength of the extract and setting up the required animals about the indicated end point on the week following. This has meant in our experience the immediate use of 20 or 25 animals for each assay of urinary prolan.

c. The degree of accuracy which can be obtained when the relatively small number of animals practical for clinical testing are used, remains the most difficult question. For the assay of urine extracts our unit was defined as the amount of prolan which when injected in the manner described will cause the formation of corpora lutea in at least three out of five rats. For the serum which was available in smaller quantities, the unit was taken at the point where two out of three animals were positive. With a group of 405 animals it was found that when half of the extract needed to show one unit was injected, 12.6 per cent of the animals were still positive; when twice this amount was used, 11.2 per cent were still negative. Such variability in response makes results based on one animal totally unreliable and those on five open to some question.

Normal Prolan Levels in Pregnancy.—The excretion of prolan undoubtedly varies greatly at different periods of pregnancy. A very high peak is encountered at about the sixtieth day after the last menstrual period when as much as 300,000 rat units may be present in a liter (Browne and Venning;[9] Evans[18]). After this, there is a gradual

decline in excretion rate, and, by the beginning of the last trimester, the levels are probably at least relatively constant. During this time Browne and Venning[9] report an output of 3,000 rat units, Smith and Smith[53] of 560 rat units in twenty-four hours, and Zondek[65] of 4,000 to 12,000 units per liter.

The average values for 17 normal patients of this study were approximately 4,000 rat units per liter of serum and 2,500 rat units for the twenty-four-hour urine specimens (see Table I).

That a given value is not by any means constant for an individual case is indicated by determinations made during successive weeks before delivery and during labor (Table II). The figures show that a single test is insufficient definitely to determine the characteristic prolan concentrations in a certain patient. There are, however, certain suggestive trends to high or low levels in each of these cases.

TABLE I. NORMAL PROLAN EXCRETION AND SERUM CONCENTRATION IN LATE PREGNANCY

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE RAT UNITS	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					500-999 R. U.	1,000-1,999 R. U.	2,000-3,999 R. U.	4,000-5,999 R. U.	6,000-10,000 R. U.
Serum prolan: Rat units per liter	37.4	17	23	3,871	0	5	5	8	5
Urine prolan: Rat units per 24 hours	37.4	17	23	2,404	5	6	8	4	0

TABLE II. VARIATIONS IN PROLAN VALUES ON SUCCESSIVE DETERMINATIONS AT WEEKLY INTERVALS

PATIENT	WEEKS OF GESTATION	RAT UNITS PER LITER OF SERUM	RAT UNITS PER 24 HOURS
I.S.	34	4,000	2,630
	35	6,667	2,880
	36	4,000	2,040
M.M.	36	1,000	700
	37	1,000	750
	38	2,000	2,000
	39	1,000	1,200
	L.	2,000	2,340
M.G.	37	6,667	4,720
	38	6,667	1,960
	39	4,000	2,420
	40	2,000	1,800
	L.	2,000	2,000
L.D.	37	8,000	2,340
	38	6,667	4,760
	39	6,667	5,200
	40	4,000	8,480
	L.	4,000	6,667

Prolan Values in Toxemias of Pregnancy.—Several reports have been made upon the serum and urinary values for prolan in the toxemias of

pregnancy. The majority of these indicate a rise in prolan but the findings are by no means uniform.

The studies of Smith and Smith must unquestionably be given the most weight. Their first paper[53] reported results on the study of 42 patients in the last trimester of pregnancy and indicated that in 96 per cent of the toxemic and eclamptic patients there was an excess of prolan. Subsequently reported studies[56, 58] by these workers confirmed their early findings by adding more cases and suggested also that a rise in the prolan of the serum occurred six weeks before the appearance of clinical manifestations of toxemia (Smith and Smith[56]), and that this fact might be of practical value in anticipating the approach of symptoms.

Besides this work just cited, scattered reports based on smaller numbers of cases have come from many sources. Ehrhardt[16] reported positive tests for prolan in the cerebrospinal fluid of eclamptics and pre-eclamptics and negative findings in the fluid of normal women. Apparent confirmation of this finding was later made by Heim[27] and by Hashimoto.[26] Reports on increases of prolan in the urine of eclamptics and pre-eclamptics have come from Heim[27] and from Bentivoglio,[7] from Anselmino and Hoffmann,[3] and from Schmidt.[48] Ehrhardt[16] has, however, reported a failure to find high prolan in either the blood or urine of eclamptics. Heim[27] reported several inconsistencies and Schmidt's[48] work, the most extensive of the German studies, indicated that in only 7 of 25 cases of eclampsia and pre-eclampsia was prolan B increased.

The results of the present studies (Table III) do not show consistent differences in the average prolan concentration in the serum or in the rates of urinary excretion between normal and toxemic patients. The figures as first averaged indicated therefore considerable disagreement with the findings of Smith and Smith.

TABLE III. PROLAN EXCRETION AND SERUM CONCENTRATION IN LATE PREGNANCY TOXEMIA

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE RAT UNITS	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					500-999 R.U.	1,000-1,999 R.U.	2,000-3,999 R.U.	4,000-5,999 R.U.	6,000-10,000 R.U.
Serum prolan: rat units per liter	34.6	20	25	3,241	2	4	8	4	7
Urine prolan: rat units per 24 hours	34.0	21	27	2,719	5	4	6	11	1

Search for a reason for this disagreement in results led to a consideration of possible differences in the classification of the toxemias of pregnancy. The Bellevue Hospital classification recognizes three groups of cases among the late toxemias: namely, eclampsia and pre-eclampsia, essential hypertension, and chronic nephritis. The latter group is extremely small in number, so that practically all patients with symptoms of hypertension or albuminuria, not known to have been present in the first trimester of pregnancy, are classed as pre-eclamptic toxemia. It was possible therefore that many of these cases classed by us as pre-eclamptic toxemia might have been regarded as chronic nephritis

TABLE IV. PROLAN IN SEVERE CASES OF PRE-ECLAMPTIC TOXEMIA*

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
Z.R.	32	v	38	++++	175/140	++	1,000	6,560	Medical induction
M.J.	32	0	28	++++	220/130	++++	6,667	1,240	Hysterotomy
H.S.	19	0	23	++++	170/110	++	----	5,200	Hysterotomy
L.S.	33	0	26	++++	176/110	++	6,667	4,160	Hysterotomy
D.M.	26	ii	24	++++	198/110	++++	2,000	3,000	Hysterotomy
			25	++++	186/110	++++	2,000	2,720	
			26	++++	190/114			4,133	
Average							4,083	4,089	

*The averages are based on the mean of the several determinations for a given patient.

TABLE V. PROLAN IN TOXEMIA WITH DEATH OF FETUS*

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
V.H.	18	0	32	++++	158/98	+++	4,000	4,040	Macerated stillbirth 12 days after first test
			33	++++	210/160	+++	----	835	
A.M.	27	0	33	0	170/110	++	2,000	985	Macerated stillbirth 31 days after first test
			37	++	150/115	++	1,000	1,250	
			38	+	140/110	+	2,000	1,310	
L.J.	27	iii	40	++	180/108	++	2,000	4,160	Macerated stillbirth 3 days after test. Fetal heart heard day of test
A.R.	29	i	39	+	168/110	+	1,000	1,205	Macerated stillbirth 10 days after first test
			40	0			1,500	810	
L.I.	26	i	32	+	118/84	++	4,000	457	Macerated stillbirth 7 weeks after first test
			36	+	174/125	+++	2,000	845	
Average							2,600	2,169	

*Only first figure is used in final averages of toxemic cases.

by other workers. We therefore selected out four special groups, each unfortunately represented by only a few cases.

1. *Severe Cases of Pre-eclamptic Toxemia.*—The first group consisted of five cases and are those severe enough to have warranted termination of the pregnancy (Table IV). The cases of this severe group had with one exception some elevation of the prolan in either the serum or the urine.

2. *Cases of Late Toxemia Culminating in Fetal Death.*—The next group included the cases in which death of the fetus occurred within a few weeks after the tests were undertaken. The fact of impending fetal death suggests a serious degree of toxemia, but it might not unreasonably be expected that associated placental

TABLE VI. PROLAN IN ECLAMPSIA

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
E.H.	39	i	28	0	210/140	+++	1,000	680	Convulsion 2 days before test. Delivery 1 day after
S.McL.	37	i	32	++++	172/96	+++	----	2,630	Patient was delivered and died next day
ALo.M.	24	0	40	+++	142/92	+	4,000	840	Post-partum convulsion and specimen

TABLE VII. PROLAN IN AVERAGE CASES OF TOXEMIA

PATIENT	AGE	PARA	WEEK OF GESTATION	CLINICAL DATA			SERUM	URINE	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER 1,000 C.C.	RAT UNITS PER DAY	
F.C.	34	iv	40	0	152/100	+	1,000	815	Very mild case
A.C.	30	iii	36	+	162/92	+++	1,000	692	Toxemia with previous baby
G.P.	20	0	40	++	158/92	++	4,000	2,570	Headaches. B.P. in labor 170/108
A.C.	30	ii	40	++	158/90	0	2,000	4,040	B.P. 170/96 in labor
L.D.	20	0	37	2.9g	145/110	++	8,000	2,340	Severe case. Induction considered
			38	3.8	170/114	++++	6,667	4,760	
			39	5.4	158/124	+++	6,667	5,200	
			40	4.2	188/118	+++	4,000	8,480	
Average							2,866	2,662	

damage would result in diminished hormone production. The prolan levels of both blood and urine were found to be lower than in the severe cases (Table V) of the last group, and the serum values were even somewhat lower than those for the normal women.

3. *Eclampsia.*—There were three cases (Table VI) which developed eclampsia. Neither of the two with convulsions ante partum showed signs of an increased prolan, although repeated specimens could not be examined. In the third case, which has not been used to compile the average values, the convulsions developed after labor. The low urinary prolan in this case is not surprising considering the rapidity with which these hormones disappear after delivery. The serum prolan in this case was perhaps a little high.

4. *Mild Pre-eclamptic Toxemia.*—The remaining cases have been classed as mild, because they were unassociated with any special complications (Table VII). In all but one case of this group the prolan was not different from the normal. One patient from whom four specimens were obtained showed consistently high levels. She was unquestionably the severest of the five and might more properly belong to the class in which termination of pregnancy was carried out.

Conclusions in regard to the prolan in the toxemic cases of this series were simply these. The general average and range for the prolan concentration of the serum and the twenty-four-hour excretion were not significantly different from those of the normal controls. Selection of the severer cases with all of the manifestations of pre-eclamptic toxemia resulted, however, in the isolation of a group in which the prolan of the urine or serum was a little high.

ESTROGEN DETERMINATIONS

Preparation of Specimen.—The amount of estrin in the urine of pregnant patients is large enough so that concentration before assay is unnecessary. The estrogens occur in the urine principally in a combined form which is not determinable by bio-assay. In order to free the combined estrogens, all urines were "hydrolyzed" by boiling for two hours after the addition of 10 per cent by volume of concentrated hydrochloric acid. The figures for the urine represent then the so-called "total estrogens." The sera were not so treated and only free estrogen was therefore determined here.

Estrogen Assay.—The assay was conducted according to the typical Allen-Doisy test on spayed female rats, weighing from 125 to 175 gm. Each rat received a "priming" dose of an estrogen ten days before the assay, and animals unresponsive to such treatment were not used. Injections for the test were given in a total of four doses on two successive days and vaginal smears made four times on the third and fourth days.

The unit adopted by us was complete cornification with complete absence of both nucleated epithelial cells and lymphocytes in three-fourths of the animals. At first four, and later eight, animals were used at each dose level. The studies of various workers have shown that the rat unit may vary from about 5 to 40 international units (Hain and Robson,[25] Hinglais and Hinglais,[30] Bülbring and Burn[11]. Repeated assay of crystalline estrone has shown that the rat unit, as defined by us for this work, has amounted to about 35 international units. This will explain why our figures for estrogens in pregnant urine are considerably lower than those reported by many other investigators.

The definition of the unit, as described, was originally adopted with a view toward increased accuracy, since it was felt that complete cornification was easier

to recognize than any special proportion of cells. There appears to be no great disadvantage in using such a large unit in the assay of the urine in pregnancy, but special difficulties occur with the serum. Here one rat unit is rarely contained in less than 5.0 c.c., and since the supply of material for testing is limited, accurate quantitative studies are not feasible. Some basis for comparison was obtained by estimating the degree of estrus reaction in each smear, and grading each with figures from 0 to 4, according to the method originally described by Frank[23] for tests on the blood of nonpregnant women. Four animals were each injected with 3.0 c.c. of serum, the height of the reaction in each noted and the average expressed by a single figure.

The accuracy of the figures for the estrogens based on rat assay is apparently less than for the prolan. This statement is based on studying the reaction of a group of 474 animals which showed that, when one rat unit is fixed as the amount which will cause complete cornification in at least 75 per cent of the animals, then with half of this dose a quarter of the animals are still positive and with double the dose, 15 per cent are still negative.

Normal Estrogen Values in Pregnancy.—The changing methods of hydrolysis, extraction and assay of estrogenic substances in the urine have resulted in continued alteration in what have been regarded as the normal values. In 1928 Aschheim and Zondek[4] reported 6,000 to 10,000 mouse units per liter in the last trimester of pregnancy. Smith and Smith's figures in 1934 before hydrolysis was used were 5,800 rat units for twenty-four hours. Since then the figures have mounted rapidly. Cohen, Marrian and Watson[13] reported by colorimetric methods a daily excretion of 22 mg. of combined estriol and 3 mg. of estrone which has an equivalent value of about 250,000 mouse units. Smith and Smith[58] give perhaps slightly higher values. Goldberger[24] found lower values for "total estrins" with a peak of 180,000 mouse units at the thirty-third week followed by a fall to from 40,000 to 45,000 mouse units during the last month. Goldberger's[24] figures indicate the marked variations which may be present in the excretion curves of even a single case, and Browne and Venning[9] suggest the occurrence of cyclical fluctuations. With the serum, the reported figures have been still less consistent, owing of course to the small amount of material available for tests. Smith and Smith[53] obtained

TABLE VIII. ESTROGEN EXCRETION AND SERUM CONCENTRATION IN LAST TRIMESTER OF NORMAL PREGNANCY

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					0-499 R.U.	500-999 R.U.	1,000-1,999 R.U.	2,000-2,999 R.U.	3,000-3,999 R.U.
Urine Rat units a day	37.4	17	23	1,311	2	8	6	5	2
Serum					SERUM. REACTION TO 3.0 C.C.				
Reaction to 3.0 c.c.	37.4	17	23	1.58	0-0.5	0.5-0.9	1.0-1.9	2.0-2.9	3-4
					4	2	5	8	4

positive reactions with 3 c.c. or less in their early reported normals. Bickenbach and Fromme[8] never obtained a positive with less than 10.0 c.c.

The twenty-four-hour excretion of "total estrin" in twenty-three assays of this study averaged 1,300 rat units (Table VIII). With the large rat unit used, this corresponds to about 45,000 international units, approximately the figure reported by Goldberger[24] for his case during the last few weeks of pregnancy. As regards serum, a full rat unit was practically never demonstrable by the injection of 3.0 c.c. of serum.

Figures obtained by repeated assay of several specimens on successive weeks again showed that wide fluctuations may occur in the rates of excretion (Table IX). The figure obtained by one determination does not therefore characterize the behavior of the estrogens for a given case.

TABLE IX. VARIATIONS IN ESTROGEN VALUES ON SUCCESSIVE DETERMINATIONS AT WEEKLY INTERVALS

PATIENT	WEEKS OF GESTATION	URINE	SERUM
		RAT UNITS PER DAY	REACTION TO 3.0 C.C.
I.S.	34	1,646	2.5
	35	1,800	1.75
	36	3,406	1.00
M.M.	36	585	2.00
	37	2,380	2.25
	38	1,300	3.25
	39	530	2.25
	L	800	2.25
M.G.	37	295	0.75
	38	245	2.50
	39	300	2.75
	40	450	1.25
	L	500	1.25
L.D.	37	585	2.20
	38	2,380	2.25
	39	1,300	3.25
	40	530	2.25
	L	166	1.25

Total Estrogens in Toxemias of Pregnancy.—Relatively low values for estrogenic hormone in the urine and blood of toxemic patients were reported by Smith and Smith[53, 56, 58] in 1934, 1935 and 1937. This coupled with the simultaneously high prolan has laid the basis for an hypothesis of an "imbalance" between the two hormones as a factor in toxemia. By means of a chemical test, Savage and Wylie[47] have corroborated the findings of low estrins in toxemic cases. They found, however, that values were low in the so-called chronic nephritics as well as in the cases of pre-eclamptic toxemia.

The summary of the results of 62 determinations in toxemic patients shown in Table X indicates what are probably significantly lower estrogen values than in the normal cases. The average figure of 584 rat units for twenty-four-hour excretion is less than half of

the normal figure. The usual reaction to 3.0 c.c. of serum was also definitely weaker in the toxic cases. Although exceptions occurred, the excretion in the toxemic cases was as a rule under 1,000 rat units, that for the normal cases usually above that figure.

TABLE X. ESTROGEN EXCRETION AND SERUM CONCENTRATION IN LATE PREGNANCY TOXEMIA

	AVERAGE WEEKS OF GESTATION	TOTAL PATIENTS	TOTAL TESTS	AVERAGE	NUMBER OF CASES IN VARIOUS RANGES OF HORMONE CONCENTRATION				
					0-499 R.U.	500-999 R.U.	1,000-1,999 R.U.	2,000-2,999 R.U.	3,000-3,999 R.U.
Urine Rat units a day	34	21	31	584	11	14	5	1	0
Serum					SERUM. REACTION TO 3.0 C.C.				
Reaction to 3.0 c.c.	34	21	30	0.92	0-0.5	0.5-0.9	1.0-1.9	2.0-2.9	3-4
					10	9	6	4	1

Separation of these cases into the four special groups previously used in reporting prolan studies showed little difference in the figures for the different classes of cases (Tables XI, XII, XIII, and XIV). There was nothing to distinguish the severe cases from the mild ones. The approaching death of the fetus was not heralded by any rise or fall in the estrogen figures. The values for urinary estrogens of the two eclamptics studied ante partum were, however, the lowest of any group. The consistent and rather wide divergence from the normal of the estrogen values in the toxemias makes it appear then that here an actual difference exists.

TABLE XI. TOTAL ESTROGENS IN SEVERE CASES OF PRE-ECLAMPSIA

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
Z.R.	32	v	38	++++	175/140	++	536	0.75	Medical induction
M.J.	32	0	28	++++	220/130	++++	1,033	0.66	Hysterotomy
H.S.	19	0	23	++++	170/110	++	325	—	Hysterotomy
L.S.	33	0	26	++++	176/110	++	336	0.00	Hysterotomy
D.M.	26	ii	24	++++	198/110	++++	225	0.25	Hysterotomy
			25	++++	186/110	++++	1,400	—	
			26	++++	190/114	++++	775		
Average							600	.45	

TABLE XII. TOTAL ESTROGENS IN TOXEMIA WITH DEATH OF FETUS

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
V.H.	18	0	32	++++	158/98	+++	835	0.50	Macerated stillbirth 12 days after first test
			33	++++	210/160	+++	840	0.50	
A.deM.	27	0	33	0	170/110	++	820	0.25	Macerated stillbirth 31 days after first test
			37	++	150/115	++	1,562	0.00	
			38	+	140/110	+	655	1.25	
L.J.	27	iii	40	++	180/108	++	1,300	0.75	Macerated stillbirth 3 days after test
A.R.	29	i	39	+	168/110	+	301	0.75	Macerated stillbirth 10 days after test
			40	0			400	0.75	
L.I.	26	i	32	+	118/84	++	846	1.00	Macerated stillbirth 7 weeks after first test
			36	+	174/125	+++	422	0.50	
Average							820	0.64	

TABLE XIII. TOTAL ESTROGENS IN ECLAMPSIA

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
E.H.	39	i	28	0	210/140	+++	377	----	Convulsion 2 days before, delivery 1 day after
S.Mc.L.	37	i	32	++++	172/96	+++	395	1.75	Delivery and death 1 day later
A.LoM.	24	0	40	+++	142/92	+	97	0.25	Post-partum specimen

EXCRETION OF PREGNANDIOL

In the past both an excess and a lack of corpus luteum have been blamed for toxemia. Treatment by corpus luteum is now being advised (Robson and Patterson[46]), and abnormal values for corpus luteum in the placentas of toxemic patients have been reported (Smith and Kennard[52]).

The isolation by Venning and Browne[62] of pregnandiol from human pregnancy urine and the recognition that this substance was an inactive excretion product of progesterone have led to the possibility

TABLE XIV. TOTAL ESTROGENS IN AVERAGE CASES OF TOXEMIA

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA			URINE	SERUM	COMMENT
				ALB.	B.P.	EDEMA	RAT UNITS PER DAY	REACTION TO 3.0 C.C.	
F.C.	34	iv	40	0	152/100	+	679	0.5	Very mild case
A.C.	30	iii	36	+	162/92	+++	345	1.00	Toxemia with previous baby
G.P.	20	0	40	+	152/92	++	643	0.25	Headaches. B.P. in labor 170/108
A.C.	30	ii	40	++	158/90	0	673	2.00	B.P. in labor 170/96
L.D.	20	0	37	2.9	145/110	++	585	2.20	Severe case. Induction considered
			38	3.8	170/114	++++	2,380	2.25	
			39	5.4	158/124	+++	1,300	3.25	
			40	4.2	188/118	+++	530	2.25	
Average							708	1.30	

that its measurement might give a practical method of studying corpus luteum function. Reports have already been made that the excretion of pregnandiol is diminished in the toxemias of pregnancy (Weil;[63] Smith and Smith[54]).

The preliminary figures of Table XV confirm these observations. It will be noted, however, that again there are exceptions and that a few toxemic patients excrete more pregnandiol than do certain normals. One case of special interest showed unusually low values preceding the death of the fetus.

TABLE XV. EXCRETION OF PREGNANDIOL

	NUMBER OF TESTS	AVERAGE DAILY EXCRETION IN MILLIGRAMS	RANGE
Normal cases	14	47.8	13.0-128.0
Toxemic cases	18	17.4	0 - 51.2

Cases of Premature Separation of the Placenta.—It has been maintained by Shute[51] that certain types of late pregnancy toxemia, associated with retroplacental hematomas, showed a high estrin in the blood serum of the patients. He reports that of 66 such cases studied by him, 82 per cent showed an excess of blood estrogens and that 85 per cent of 39 cases of severe abruptio placentae also showed such an excess. Heim has reported high values for urinary prolan in cases of premature separation of the placenta.

In Table XVI are given the values for prolan and estrogen in 8 cases of bleeding of unexplained origin, probably due to minor de-

TABLE XVI. PROLAN AND ESTROGENS IN CASES OF UTERINE BLEEDING

PATIENT	AGE	PARA	WEEKS OF GESTATION	CLINICAL DATA		PROLAN		ESTROGENS		COMMENT
				ALB.	B.P.	SERUM	URINE	URINE	SERUM	
M.S.	24	i	36 37	0 0	108/70 115/70	4,000 6,667	3,136 1,813	1,306 906	1.0 0.75	Slight bleeding at 32 weeks and at onset of labor
P.N.	18	i	38	0	116/78	4,000	8,744	729	1.75	Bled intermittently 6 weeks before labor
I.D.	29	0	28	0	118/68	1,000	1,810	452	1.00	Bled constantly 6 weeks before labor
M.N.	22	0	20	0	110/68	1,666	1,136	4,284	0.25	Bled 4 weeks at 18 weeks
M.N.	24	iv	26	0	110/76	2,000	1,810	754	0.50	Bled at 24 weeks
S.F.	22	0	30	0	106/70	2,000	1,335	293	0.25	Bled constantly 1 month before test
F.R.	19	0	40	0	110/60	4,000	2,555	1,916	3.75	Bled 7 days before labor
M.B.	21	ii	32	0	120/68	1,000	4,680	780	1.50	Bled constantly from 35th week
Average of mild cases						2,625	3,068	789	1.26	
M.D.	43	xi	32	+	160/106	4,000	4,257	212	0.25	Premature separation. Stillbirth
R.F.	21	0	35	++++	130/98	4,235	----	----	1.00	Complete separation. Stillbirth

grees of placental separation, and in 2 cases of typical complete separation of the placenta. There is no evidence of excessive estrogen in any of these patients. It is not certain, however, that this group is clinically identical with that described by Shute as being characteristically associated with an excess of estrogen.

DISCUSSION

The significance of these hormone differences between normal and toxemic patients is still a matter for theory. According to one view a disturbed balance between hormones may actually be the cause of toxemia. A simpler view is that the abnormalities are merely the result of the disordered physiology of the toxemic patient.

The excretion of the estrogens for example is dependent upon a great variety of conditions. There is first the rate of production which occurs in the placenta. There is second the degree of destruction or conversion into an inactive form which may occur in the liver or kidney. There is finally the factor of kidney excretion, although there is less belief than formerly in a renal threshold. With the amount of estrogen in the urine dependent on placental, renal, and hepatic function, it is not surprising that the values in blood and urine may be altered in such a disease as pre-eclamptic toxemia. Somewhat similar conditions undoubtedly govern urinary pregnandiol values, and probably blood and urinary prolan concentration.

CONCLUSIONS

1. In a broad sense there can be little doubt that the placental hormones are a factor in the late toxemias of pregnancy.
2. The tests for these hormones give only approximate values.
3. The blood and urinary figures for these substances show large normal variations when different individuals are compared and even when different specimens of the same individual are contrasted.
4. In a series of 21 cases of late toxemia and 17 cases of normal pregnancy, there was evidence of a frequent but not invariable lowering of the estrogen values in the toxemic cases and of an elevation of the prolan values in a few cases only. A lowered pregnandiol excretion was also noted in a shorter series of determinations.
5. No hormone abnormalities were noted in 8 cases of unexplained bleeding and two cases of premature separation of the placenta.
6. The hormone changes observed in the toxemic patients are perhaps associated with the cause of toxemia, but may simply be the result of the disturbance of kidney, liver, or placental physiology.

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DISCUSSION

DR. CARL R. MOORE.—I am certainly glad to be one of you to congratulate Dr. Taylor on his conservatism—conservatism not only in handling the theoretical aspects of such a problem as he presented but likewise in handling the data which he has collected in an endeavor to throw light upon a particularly difficult problem. Conservatism and hard work are the two greatest needs, it seems to me, in such a field as this. Conservatism, if for no other reason than the fact that in this more or less newly developed field of hormones, some have had hopes that many baffling problems, unsettled before, would be settled by the new technique. For this reason we must obviously consider these problems with a great deal of open-mindedness and not make an attempted analysis with preconceived ideas. As you know, hormones have been looked to to cure practically everything from temperamental disturbances to wrinkles on the face and defects in hearing. Hormones do alter the physiology of the organism and abnormal physiology does alter hormone secretion.

In an attempt to analyze Dr. Taylor's paper there are just two main aspects I wish to mention. It seems to me that he has very adequately considered the theoretical aspects, or the possible bearing of the hormones in relation to the conditions he is describing. Obviously you would not expect one such as myself, who works with

rats, guinea pigs, and other low forms, to be very well versed on the treatment of eclampsia, because we do not encounter such disturbances in our experimental material. We are very thankful that we can carry out hormone studies in animals that are normal or modified by our choice. We do not work with sick animals; we discard them. Dr. Taylor has apparently considered very carefully the possible angles on the physiological side, that is, the bearing of the hormones on this disease. I am certainly not in position to suggest any which he has omitted.

The second point that I wish to emphasize clearly in your minds is that Dr. Taylor has not tried to prove that hormones cause eclampsia or that any one hormone causes eclampsia, he has merely attempted to determine whether there is a deviation in hormonal output detectable in individuals showing this condition when compared with those whose pregnancy is normal. If he had been able to demonstrate that there were gross differences he still would not be in position to maintain that the different hormonal condition was the cause of the underlying condition. He has very emphatically pointed out that excessive hormone output might be merely an accompanying condition and not the cause.

I have found Dr. Taylor's talk so satisfying that I do not seem able to criticize the many approaches he has considered as bearing on the theoretical aspects. There is one point that should be considered if real progress is to be made in this field. Only those of you who have attempted to make this type of analysis realize the multitude of difficulties in arriving at trustworthy results. Dr. Taylor has pointed out that it is impossible for any one individual to take any other individual's findings because standards of procedure and end points differ so widely. It would seem that not only in this but in many other diseases of this kind cooperative work would be well worth while, in which a central agency would handle all the analyses. Working even with normal animals on two sides of the Atlantic Ocean very different results are reported, not because the animals are so different but because different methods of procedure, such as treatments, extractions and assays, are so at variance. Cooperative projects would seem very much worth while.

I am not certain whether Dr. Taylor has not been too conservative. I have commended him for it, but often averages are sometimes very misleading. After all we must depend on averages until we have clear-cut results. A small number of cases in which variations of from 800 to 1,000 per cent are included may completely eliminate any suggestions indicated in the collection of data when only averages are considered. It is obvious that more cases are needed. One could well use a graph of findings from 100 normal women, not in the thirty-fourth week but in all weeks of pregnancy and perhaps have a reliable standard of reference with which to compare hormonal assays from pathologic cases. Such cooperative projects could be established in large cities. A great deal can be said for a cooperative project carried out by one set of investigators as a foundation for establishing basic principles which are needed to answer the question, not whether these hormones are the cause of this condition, but merely whether they vary from the norm found during normal pregnancy. Dr. Taylor has carried out a great deal of work but he has been compelled to report to you only negative results. He has been unable to settle one point firmly in his own mind with this work, Is there a difference between the normal condition and the pathologic one from the standpoint of the output of these individual hormones? It is perfectly obvious that a discussion of results of different investigators which are not comparable is futile and utterly useless. It is also perfectly obvious, I think, that great advances would be made if we could reproduce in some suitable animal the experimental condition now under consideration, but so far as I know there is little hope of its accomplishment.

DR. WILLIAM J. DIECKMANN.—Innumerable attempts have been made during the past few decades to link eclampsia with an abnormal function of one or more of the glands of internal secretion. The rapidity with which an eclamptic patient may recover is well known, and the pathologic changes, if present, are usually too meager to account for the many signs and symptoms of the disease and the marked physical and chemical alteration in the blood, urine, and tissues. The most logical theory is that eclampsia is caused by a disturbance in the normal physiology of an

organ or a gland. Such a condition could respond to treatment very quickly. Thus, the idea of a hormonal imbalance is intriguing.

It seems to be the consensus of opinion, although the amount of accumulative data is relatively small, that eclampsia and pre-eclampsia are characterized by a low estrogen and high prolan concentration in both blood and urine. Smith and Smith in their last report state that "the manifestations of pre-eclampsia coincide with changes in the urinary values for pregnandiol, estrone, estriol, and estradiol which reflect a progestin deficient metabolism of the estrogens." They suggest "that the vascular phenomena which are responsible for endometrial flow and pre-eclampsia may be brought about by a toxic concentration of nonestrogenic breakdown products resulting from destruction of the estrogens." They have treated several presumably pre-eclamptic patients one of whom received 170 mg. of progesterone and 2,550,000 I.U. of estradiol benzoate over a period of nine days without any clinical change. Incidentally the cost of these substances would amount to $382.00. Dr. Taylor has been very conservative in his conclusions, stating that the test for hormones gives only approximate values and that the changes may perhaps be associated with the cause of toxemia or they may be the result of the disturbances of kidney, liver, or placental physiology.

The work of Thorn and Harrop and of Kenyon and co-workers lends some support to the theory that a disturbance of the hormone balance may be associated with pre-eclampsia. These investigators noted that a retention of sodium together with associated water may be produced in both dog and man by the administration of estrone, estradiol, progesterone, pregnandiol, and testosterone. The retention was sufficient to produce an increase in body weight. Similarly, the increase in weight often seen before menstruation may possibly be due to the alteration in concentration of these hormones.

Stander has reported marked changes in the uric acid, lactic acid, and CO_2 content of the blood in toxemic patients. We have emphasized the marked alterations in blood and plasma volume and changes in concentration of serum protein, hemoglobin, etc., and correlated these changes with the clinical condition of the patient. Some investigators have attributed eclampsia and pre-eclampsia to these physicochemical changes. In view of these extensive alterations it is not improbable that the hormones are also affected, and the changes in concentration and excretion may be, as also suggested by Taylor, a result instead of a cause of pre-eclampsia.

The obstetrician has not decided what eclampsia, pre-eclampsia, or toxemia of pregnancy are either clinically or pathologically, and yet he has been observing these conditions for many years. I have been especially interested in the study of the toxemias of pregnancy for the past fifteen years, and yet my diagnoses as to type have frequently been incorrect especially if made during the hospital period. None of the published reports of hormone studies have followed patients long enough after delivery to confirm their diagnosis of the kind of toxemia. Furthermore, I believe the same patient should be followed through a subsequent pregnancy to determine if the hormone assays are again abnormal or normal.

Eclampsia according to Küstner can be cured with thyroxin. Hoffmann and Anselmino have stated that the thyroid hormone content is tremendously increased in the blood of eclamptic patients. We have found daily doses of 1 or 2 gr. of thyroid to be of no value in pre-eclampsia, perhaps because this condition does not permit protracted medical treatment. However, in the patient with vascular-renal disease with marked albuminuria, thyroid therapy seems to be of some value in reducing, or at least preventing further increase in the amount of protein excreted per 24 hours; other therapeutic measures are also used. Nicholson has stated that the more normal the thyroid the less likely that toxemia will develop. Approximately 7 per cent of our toxemic patients had hyperthyroidism; the diagnosis of toxemia was based primarily upon the hypertension which was usually present in these patients.

The adrenal cortex enlarges in pregnant animals, and it has been stated that the hypertension of toxemia is due to an increased amount of adrenalin. Adrenal cortical extract because of its effect in increasing blood and plasma volume and also its effect on the renal threshold for sodium has been suggested in the treatment of eclampsia, but, so far as I know, has not been used.

Cushing described an invasion of basophilic cells from the anterior lobe and pars intermedia of the pituitary into the posterior lobe. He postulated that vasopressin came from the anterior lobe because the posterior lobe does not look like secreting tissue. All reports to date do not confirm Cushing's theory. The anterior lobe of the pituitary does enlarge during pregnancy, but no one has noted any unusual change in association with toxemia of pregnancy. Cushing's comment that the posterior lobe does not look like secreting tissue is interesting because certainly the placenta does not look like an organ of internal secretion, and yet it is supposed to produce enormous quantities of female hormones.

Anselmino and Hoffmann stated that there was an increased amount of the presso- and antidiuretic components of the posterior lobe secretion in the blood of eclamptic and severe pre-eclamptic patients. However, five groups of investigators have been unable to confirm this work. Michel and I stated that the blood pressure of the true eclamptic and pre-eclamptic patient gave a marked rise if the patient was injected with two minims of pituitrin. All other nonpregnant and pregnant patients, even if the latter had essential hypertension or vascular-renal disease, gave little or no response. This test has been used by us to aid in the differential diagnosis of pre-eclampsia from other toxemic conditions. Our work has been used to support theories as to the cause of eclampsia which ascribed the disease to posterior lobe hormones, but the mere fact that pre-eclamptic patients show an unusual response to the injection of pituitrin does not warrant the statement that eclampsia is due to an abnormal amount of posterior lobe secretion.

According to the chemists' conception the hormone studies to date are not quantitative but are roughly qualitative. However, they offer possibilities as to the diagnosis of pre-eclampsia when it is present and also a possible means of detecting patients who may develop pre-eclampsia. It is unwarranted to draw conclusions from a study of 50 or 100 cases when the methods of analysis are crude and the variation in both normal and abnormal overlap. Furthermore, to treat toxemic patients with hormones and other drugs and ascribe improvement only to the hormone is incorrect. The clinical condition of toxemic patients is so variable that a large number must be treated with *only* the hormone in question before any conclusions are justified.

DR. FRED L. ADAIR.—I would like to compliment Dr. Taylor on the excellence of his material and its presentation. I would like to mention the parathyroids in connection with a consideration of hormones in their relations to the toxemias and metabolism of pregnancy. There is a case in the literature in which thyroidectomy was done and the parathyroids injured. The patient was operated upon after three normal pregnancies. During the subsequent pregnancy she developed tetany which was controlled by the use of parathormone. Dr. Laura DaSef and Dr. Bengt Hamilton made a study of parathyroids in pregnancy in our clinic, indicating that there are certain definite parathyroid changes during pregnancy shown by an increase of parathormone during pregnancy. We have made no such thorough study as Dr. Taylor has made of the hormones. However, we have done some work, and with the permission of the Chairman, I would like to ask the courtesy of having Dr. Ruth Watts discuss it.

DR. RUTH WATTS, PH.D.—I wish to join Dr. Moore in commending Dr. Taylor for his scientific approach to a problem in a field in which the literature is so filled with data of little significance.

I wish to add a point or two in review of Smith's work. If you inspect his work you will find that the individual variation in both groups is very great. The standard deviation in such groups can become as large as the value itself. It then becomes impossible to evaluate a single determination by comparison with a mean value unless that value is an extreme one. I have some slides to show, some results of a study Dr. Adair and I have undertaken. I am showing the first one for two reasons, first, to confirm Dr. Taylor's survey on relation of dose to response, and the second, to present our method of assay because I want you to judge the reliability of our data.

We have assayed each of the gonadotropic and estrogenic hormones by the characteristic curve method; two consecutive twenty-four-hour urine specimens were assayed for each individual; twenty 21-day-old rats were used in the prolan assay and 40 castrated rats for the assay of estrogenic hormone. After injecting the entire group of animals at one dose level, the assay value was obtained by reading from the chart the value corresponding to the percentage response.

The second chart is a graphic presentation of the actual values (R.U. per twenty-four hours) obtained in our study. There is a marked tendency toward the increased excretion of gonadotropic substance and a decreased excretion of estrogenic substance in the toxemic group. Although the mean values show a definite difference between the normal and the toxemic groups the extreme variation in the individual values composing these groups makes it impossible to compare safely an individual determination with this mean value. In the normal group there seems to be a relation between the amount of gonadotropic and estrogenic hormone excreted by each individual, i.e., an individual excreting a relatively large amount of one will also excrete a relatively large amount of the other. This is illustrated in the chart by the slope of the line connecting those two values for each individual. The chart is constructed so that in the normal group the scale of the range of the twenty-four-hour values of estrogenic substance is equal to the scale of the range of the twenty-four-hour values of prolan. In the toxemic group the general slope of these lines is altered and assumes an opposite direction.

In the next chart, this relationship is expressed as a ratio of the excretion of prolan to estrogenic substance. The hormone analyses expressed in terms of this ratio seem to show less variability due to individual variation than was shown in the previous chart. These ratios are fairly constant in the normal group and are definitely increased in the toxemic group.

In conclusion, our work shows great variation in actual values of gonadotropic and estrogenic substances, a fairly constant ratio between these two substances during normal pregnancy and an increase in the ratio during pregnancy in the toxemic group.

DR. ALEXANDER GABRIELIANZ.—In Dr. Taylor's paper there is a statement about pituitary and pituitary-like substances as if they were the same substances. In my opinion there is a great biologic difference between the two. If an immature hypophysectomized mouse is injected with pituitary-like substance, without reference to dosage, a follicle never appears on the ovary, but if pituitary substance is injected into an immature hypophysectomized mouse, then a follicle appears on that ovary. I wish to ask Dr. Taylor if he noticed any other difference between these two, pituitary substance and pituitary-like substance.

DR. HOWARD C. TAYLOR, JR. (closing).—Dr. Moore's suggestion that hormone studies of this type should be developed as a cooperative project seems to me most important. The technical work of assay ought perhaps to be done in a department of zoology, rather than in one of medicine. It is clearly work for which the biologist is better equipped than the physician. Such investigations could be well handled by two such departments, the physician diagnosing and following the case clinically, the biologist helping to outline the experiment and supervising or performing the work of assay. With the clinician such biologic studies are a heavy burden, and a somewhat unfamiliar one, to be carried in addition to the regular work of the ward and practice.

I am very much interested in Dr. Watts' determinations. My understanding is that she found a high prolan and a low estrin in most cases, but that she also noticed several exceptions. This is of course in confirmation of much previously reported work, and especially significant since the prolan was determined by a different end object from the one usually employed. The concept of an "imbalance" is, however, in my opinion a very misleading one. It implies some sort of a reciprocal physiologic relationship between these two substances, and there is little reason yet to think that such a definite relationship exists. Absolute values are significant but I do not think that a quantitative relationship of one to the other is yet established.

I did not say that pituitary-like substance of pregnancy urine and true gonadotropic substance were identical. I was speaking of prolan A and B, which are both reactions occurring after the injection of pregnancy urine. I showed on my slide four different ovaries, one which showed no follicle, and came from an untreated infantile rat; one which showed many small follicles following injection of menopause urine; one with a single large follicle from the injection of pregnancy urine, and one with a corpus luteum, also following the injection of pregnancy urine. Whether one will get a large follicle or a corpus luteum following the injection of pregnancy urine depends, in part at least, on the amount of substance injected. There will be a very large difference in the number of units of pregnancy urine gonadotropic substance reported depending on whether one takes as an end point follicle ripening (prolan A) or corpus luteum formation (prolan B). The latter is a much more reliable end point, because partly ripened follicles may begin to occur normally in quite young rats and mice.

VESICOVAGINAL FISTULA AFTER COMPLETE ABDOMINAL HYSTERECTOMY

Description of Technique Used for the Cure of Two Cases by the Vaginal Route

Albert H. Aldridge, B.S., M.D., F.A.C.S., New York, N. Y.
(From the Clinic of the Woman's Hospital)

IN RECENT years numerous articles have appeared describing improvements in the operative technique of complete abdominal hysterectomy. The advantages of this procedure over subtotal or supravaginal hysterectomy have been emphasized and some gynecologists have been so impressed with its benefits that they have adopted complete hysterectomy as a routine procedure in cases demanding removal of the corpus uteri.

Experience with large series of complete hysterectomies will ultimately determine whether this more extensive operation, as a more or less routine procedure, is justifiable. When examination of the cervix reveals extensive birth injuries or marked chronic infection associated with conditions demanding removal of the corpus uteri, there can usually be no argument against complete hysterectomy. However, experience has shown that the milder cervical infections and erosions can be readily cured by electrocoagulation at the same time that supravaginal hysterectomy is done. By combining these two procedures complete removal of the uterus is frequently unnecessary.

It can hardly be denied that complete removal of the uterus is, on the whole, technically much more difficult than the supravaginal procedure and that the operation is attended by a somewhat higher incidence of accidents and unavoidable complications.

Among the most distressing of these is that which results in urinary incontinence from injuries to the bladder. Vesicovaginal fistula may be the result of faulty surgical technique or may occasionally be caused by conditions beyond the control of the most competent surgeon.

When vesicovaginal fistula occurs following complete hysterectomy, it is usually the result of trauma at the time of operation or secondary necrosis and sloughing of tissue about the vaginal vault and base of the

bladder. Postoperative tissue destruction in this area may be caused by infection and/or trophic disturbances from lack of adequate blood supply.

Vesicovaginal fistulas following complete hysterectomy are usually located in the vaginal vault and are invariably difficult to close. Technical difficulties of such operations include:

1. Inaccessibility of the fistulas on account of their location.
2. Fixation of the structures about the vaginal vault and fistulas which result from healing in the presence of infection, tissue necrosis and irritation caused by constant leakage of urine.

Before attempting the closure of such a fistula it is essential to allow sufficient time for complete healing of the tissues about the fistula. When the operation is done, the structures should be as clean and free from infection and induration as possible—this usually requires from three to six months. Healing can frequently be promoted by vaginal douches and local treatments with mild antiseptics. Furthermore operation should not be done until the extent and exact location of the fistula is determined by careful vaginal and cystoscopic examinations. By this precaution ureteral injury at the time of operation may be avoided.

Finally it is important for the operator to determine the most suitable position of the patient for exposure of the fistula at the time of operation and to choose an operative technique best suited for the type of fistula to be closed. Although such fistulas can usually be closed through the vagina, some operators prefer the transvesical route. It is admitted that the latter approach may be preferable in some cases. However, it is not the purpose of this report to discuss the advantages of the two methods of approach but rather to describe a surgical technique whereby two patients with large fistulas were cured by the vaginal route.

In some cases, the classical Sims' position offers the best means of exposing the fistulas. In others satisfactory exposure can be attained in the lithotomy position. Perineotomy, or the Schuchardt incision described by Ward, is useful in nulliparous women and in those in whom the caliber of the vagina is small or is constricted by scar tissue. The lithotomy position was used for the two cases to be reported. As both patients were multiparous women, vaginal incisions were unnecessary.

Numerous surgical techniques have been described for the closure of vaginal fistulas. In general these techniques fall into two classes.

Statistics show that the classical Sims' technique is attended by the highest incidence of success. By this technique the margins of the fistulas are denuded and closed with silver wire sutures. This technique is admirably suited for fistulas which occur on more or less flat surfaces. However, fistulas, in the vaginal vault, are frequently located in a distinct angle between the anterior and posterior vaginal walls. Under such conditions, the Sims' technique is difficult to apply as it is almost impossible to bring the denuded surfaces into exact apposition. If this cannot be accomplished satisfactorily, wound healing cannot be assured.

All other techniques fall into a group in which closure of the fistulas is accomplished by free dissection of the vaginal wall, excision of scar

tissue, mobilization of the bladder, closure of the opening in the bladder wall, and careful closure of the vaginal wall in one or more layers.

In closing fistulas with such techniques, an effort is frequently made to displace the closed defect in the bladder wall by sutures so placed that it does not lie directly beneath the line of suture in the vaginal wall. By this means more certain healing is assured.

In 1918 Rawls described his so-called "fascia lapping" technique for the cure of cystocele. Later he recommended adaptation of the same procedure for the cure of vesicovaginal fistula. This operation which requires careful, painstaking dissection of the anterior vaginal wall was subsequently modified and simplified by Bissell. In the past year Grad described the Bissell technique and reported a series of 100 cases of cystocele operated upon by this method.

The Bissell modification of the Rawls technique for the cure of cystocele was utilized and adapted for the closure of the two fistulas which I wish to report.

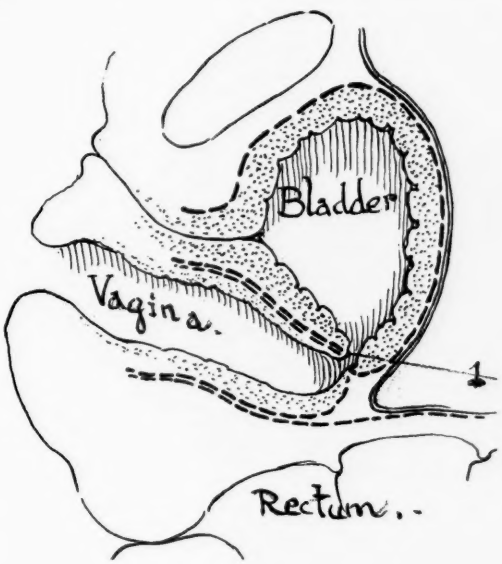


Fig. 1.

TECHNIQUE

Figs. 1 to 6 demonstrate the various steps in the operative procedure which was used to cure large postoperative vesicovaginal fistulas in the two patients whose histories are recorded with this report.

Fig. 1 is a diagram showing the anatomic relationship of the structures about a vesicovaginal fistula which occurs following complete abdominal hysterectomy. It will be noted that the muscular walls of the bladder, and the rectum, and the musculofascial wall of the vagina are completely surrounded by layers of endopelvic fascia indicated by the dotted lines. In opening the anterior or posterior vaginal walls, by midline incisions, experience has shown that free, avascular spaces between the endopelvic fascial coverings of the bladder or rectal musculature and that surrounding the musculofascial walls of the vagina can readily be entered. Dissections are always carried out in these spaces.

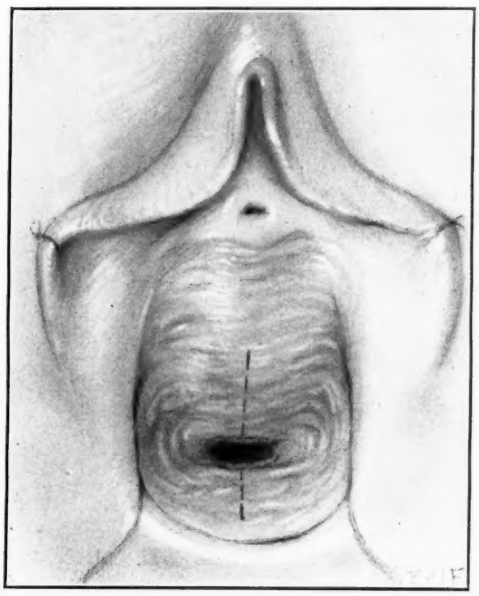


Fig. 2.

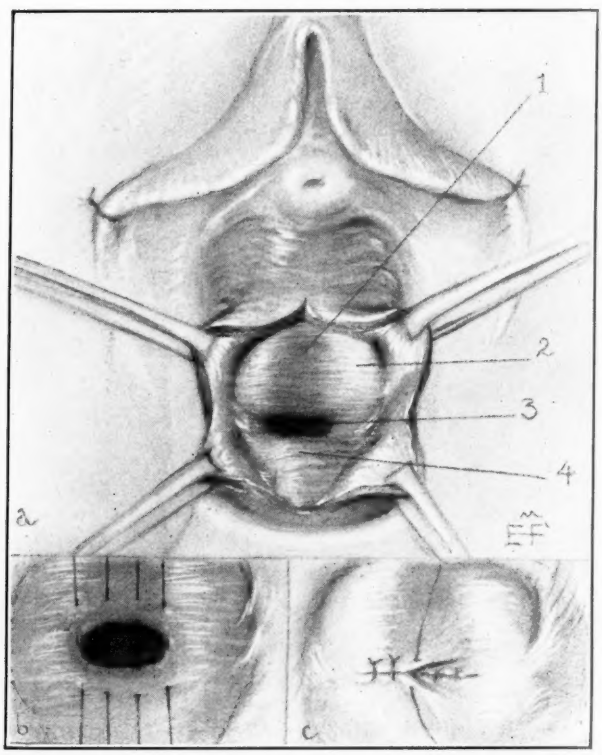


Fig. 3.

Fig. 2 shows the fistula and the dotted lines show the location of the original midline incisions used to open the anterior and posterior vaginal walls. After the proper planes of cleavage have been entered the incisions are continued around the fistula detaching the vaginal walls from its margin.

By blunt dissection the vaginal walls are then freely separated from the rectum, the bladder and the margins of the fistula, as shown in Fig. 3, *a*. In this diagram the margins of the vaginal walls are retracted to show the opening in the bladder, Fig. 3, *a-3;* the wall of the bladder, Fig. 3, *a-1,* and the wall of the rectum Fig. 3, *a-4.*

After all scar tissue has been excised from the margins of the fistula, the opening in the muscular wall of the bladder is closed with interrupted chromic catgut No. 1 sutures placed as shown in Fig. 3, *b* and re-enforced with a second infolding layer as shown in Fig. 3, *c*.

If dissection has been carried out in the proper planes of cleavage, as described above, the endopelvic fascial coverings of the bladder and rectal musculature, Fig. 4, *1* and Fig. 4, *3*, can readily be identified as smooth glistening tissue intimately covering and attached to the muscular walls of the exposed surfaces of these structures.

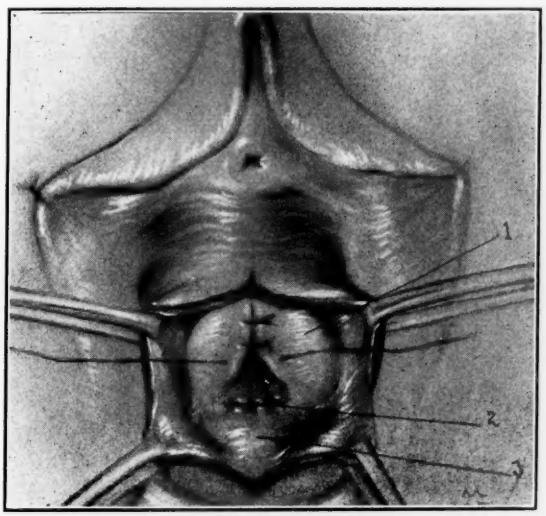


Fig. 4.

As a result of birth injury, the endopelvic fascial coverings of the bladder and rectum are frequently injured in the midline, and their torn margins are retracted laterally in both directions. Therefore, it may be necessary to pick up the margins of this layer of fascia in the sulci between the retracted vaginal walls and exposed surfaces of the bladder and rectum. Davies has recently emphasized the importance of utilizing this layer of fascia for the cure of cystocele.

When the margins of this fascial layer have been identified they are brought into apposition in the midline by interrupted sutures of chromic catgut No. 1, Fig. 4, thereby completely covering the aperture in the bladder wall which has already been closed as described above.

The vaginal walls are then utilized to complete the closure exactly as in the Bissell modification of the Rawls operation for cystocele. The vaginal mucous membrane is denuded from the right flap of vaginal wall Fig. 5, *1,* and the denuded wall is then drawn well beneath the left flap by interrupted mattress sutures of chromic catgut No. 2, as shown in Fig. 5.

The left flap is then fixed over the denuded area on the right flap by interrupted chromic catgut No. 2 sutures, as shown in Fig. 6.

By this procedure therefore the fistulous opening in the bladder is closed with two layers of sutures in the bladder musculature, and the closure is then re-enforced by superimposing the repaired endopelvic fascia and two layers of vaginal wall.

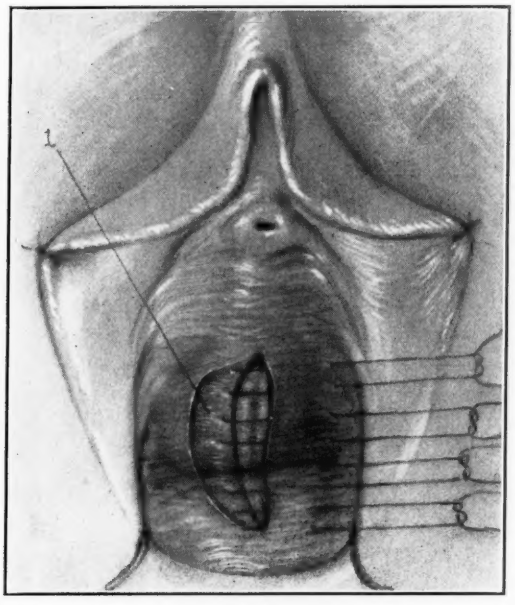


Fig. 5.

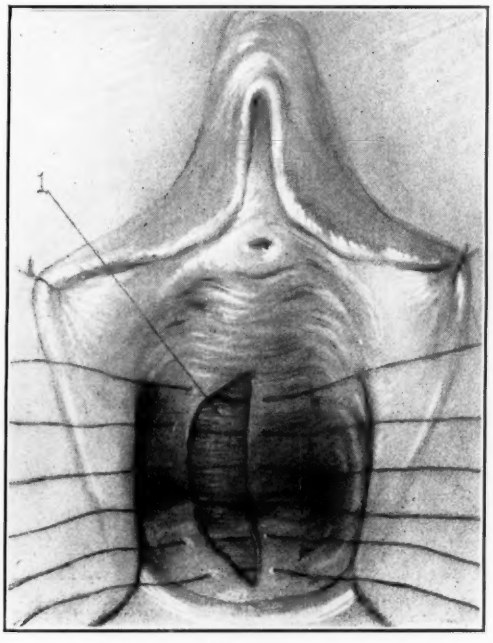


Fig. 6.

The history of the two cases which I wish to report is as follows:

CASE 1.—Mrs. L. M. (No. 56982), aged 39 years, was admitted to the Woman's Hospital on April 25, 1934, complaining of pelvic pain, leucorrhea, and menorrhagia. She had been married fourteen years, had had two pregnancies and spontaneous deliveries. The first labor lasted thirty-six hours. The medical and surgical histories were essentially negative. The blood pressure, urine and blood examinations were all negative.

Pelvic examination revealed a second degree laceration of the pelvic floor, a small rectocele, a small cystocele, a deep stellate laceration of the cervix extending to the vaginal wall on all sides associated with erosion, marked chronic infection and hypertrophy of the cervix. The uterus showed a mass of fibroids the size of a sixteen weeks' pregnancy. The tubes and ovaries were normal. At operation at the Woman's Hospital on April 26, 1934, a complete hysterectomy was done and the appendix, which showed chronic inflammation, was removed. When the uterus was excised from the vaginal vault, it was noted that the vaginal wall, when detached from the cervix, was edematous, sclerotic, and unusually thickened.

The vaginal vault was closed with interrupted sutures of chromic catgut and the detached fascial supports of the uterus were fixed to the vaginal vault. In doing the hysterectomy, no unusual difficulty was encountered in detaching the bladder from the uterus and vagina and so far as was known there was no suspicion of injury to the bladder during the course of the operation.

The highest postoperative temperature was 100.2° F. by rectum. The temperature did not exceed 99.6° F. from the second until the sixteenth day when the patient was discharged from the hospital. The patient was catheterized four times after operation and from then on emptied the bladder spontaneously. On the eleventh postoperative day she passed urine by vagina and was partially incontinent from then until she was discharged. Examination showed an extensive grayish yellow slough in the vaginal vault. This slough gradually separated leaving a vesicovaginal fistula about 2 cm. in diameter exactly in the midline in the vault of the vagina. On account of the relaxation of the vaginal walls, the opening into the bladder could be easily visualized. Healing and shrinking of the tissues about the vaginal vault was so slow that operation to close the fistula was postponed until five months after the first operation. The condition was treated with douches and local antiseptics. When the second operation was undertaken, the tissues appeared clean and free of inflammation.

On Oct. 2, 1934, the fistula was closed by the technique just described. The bladder was drained by retention catheter for ten days and the patient was discharged as cured on the sixteenth postoperative day. Her highest postoperative temperature was 100° F. by rectum. The temperature was normal after the third postoperative day. Subsequent examinations showed a satisfactory result with no apparent shortening of the vagina. It is believed that the postoperative fistula was due to delayed tissue necrosis and slough caused by infection and trophic tissue disturbances.

CASE 2.—Mrs. F. B. (No. 65169), American, aged 39, graduate nurse. Father died of cancer. She had been married twice. She had had one pregnancy and forceps delivery of large baby, weight not known, during first marriage. She had repair of birth injuries and post-partum hemorrhage following this delivery. During the second marriage she had four spontaneous deliveries and one forceps delivery; no abortions. Patient gave a history of having had tonsillectomy in 1912, hospital treatment for "peritonitis" 1932, and seven major abdominal operations for the following conditions: 1918 umbilical hernia, 1927 ulcer of stomach and gastroenterostomy, 1929 ovarian cyst, 1931 peritoneal adhesions, 1935 ovarian cyst, January, 1936 exploratory laparotomy, November, 1936 fibroids, complete abdominal hysterectomy. Had retention of urine requiring catheterization for two weeks before last operation. Stated last operation, complete hysterectomy, was very difficult and that she was on operating table for five hours. She stated that the bladder was drained with retention catheter following this operation, that she leaked urine through the vagina from time of this operation, and that she has had complete incontinence of urine, since this last operation. She passes no urine through the urethra and has

been compelled to wear pads constantly for the ten months since operation. From the history of this operation she apparently had an injury to the bladder at the time of operation and an extensive postoperative pelvic cellulitis. During the ten months she passed blood at times and in July, two months before admission to the hospital, had a severe vaginal hemorrhage which required vaginal packing by an ambulance surgeon.

Examination on admission showed a moderately obese, fairly healthy appearing woman. The general physical examination showed nothing remarkable. The blood count, blood Wassermann and blood sedimentation rate were normal. The abdominal wall showed the scars of numerous healed incisions. Some of the abdominal wounds had apparently been infected and, when healed, had left a mass of scar tissue over a large area between the pubic crest and umbilicus. Vaginal examination showed a deep vagina with a constant leaking of urine through an opening in the vault just to the right of the midline. Without anesthesia the fistulous opening could not be easily visualized by vagina.

Vaginal and cystoscopic examinations showed the vesicovaginal fistula to be at least 2 cm. in diameter slightly to the right of the midline and above the trigone of the bladder. No evidence of neoplasm of the vaginal vault or bladder could be found to account for the bleeding which had been profuse on one occasion. Bleeding had probably come from granulation tissue.

The vaginal vault was fixed by dense scar tissue. The tissues about the vault were somewhat thickened and the mucous membrane was quite reddened and excoriated from the constant leakage of urine.

After five days' rest in the hospital, the fistula was closed on Sept. 22, 1937, by the technique just described. The operation was complicated by the difficulty of exposing the area due to a deep vagina and fixation of structures about the vaginal vault. A retention catheter was left in the bladder for eight days. Following the operation the patient had a rather severe reaction with temperature to 105.4° F. by rectum and a moderate bronchitis for several days. On the fifth day she was transfused with 600 c.c. of blood. The temperature was normal after the tenth day, and she was discharged apparently cured after sixteen days. Examination at time of discharge showed no appreciable shortening of the vagina.

The patient was seen in the follow-up clinic on Nov. 24, 1937, two months after operation. The fistula was solidly healed, and the patient was entirely free of bladder symptoms. The vagina measured 10 cm. in depth.

CONCLUSIONS

1. Complete abdominal hysterectomy is accompanied by an incidence of urinary tract injuries and complications which can be reduced if, unless necessary, only the corpus uteri is removed.

2. Postoperative vesicovaginal fistula is one of the less frequent but most distressing complications which may follow complete abdominal hysterectomy.

3. The Bissell modification of the Rawls technique for the cure of cystocele can be effectively adapted for the closure of certain vesicovaginal fistulas.

33 East Sixty-Eighth Street

FETAL AND NEONATAL DISEASE AND DEATH*

FRED L. ADAIR, M.D., AND EDITH L. POTTER, M.D., CHICAGO, ILL.
(From the Department of Obstetrics and Gynecology, University of Chicago.)

IT IS often difficult for adults to realize that the diseases with which they are afflicted may arise from factors determined before birth, and in some instances even before conception. A battle is still waged between those who believe that heredity is the main factor in determining the pattern of individual existence and those who believe that it is largely limited by environmental states. It is frequently forgotten however that environment antedates birth and that it affects not only the embryo or fetus in utero but also the germ cells before their discharge from the gonads.

Abnormalities leading to defects of development, disease or death, which have their origin in the preconceptional state may be due to transmissible factors present in the genes and predetermined by specific ancestry; they may be caused by noninherited defects of germ plasm due to initial imperfections in the germ cell or they may be due to unpropitious environmental states which modify the original character of the ovum or spermatozoon.

In the first group fall such known transmissible pathologic conditions as hemophilia, polydactylism, albinism, etc. In addition to inheritance of body build and facial characteristics it is most reasonable to believe that the structure of organs and their potential capacity for growth and function are in part at least also determined by inheritance. Pearl has conclusively shown that the best way to live to old age is to be born of parents and grandparents who were octogenarians.

Environmental states affecting the germ cells include the entire physiologic mechanism of the individual. Abnormal hormonal states may interfere with normal maturation of the ovum or may inhibit fertilization after expulsion from the ovary. Extraneous influences, of which the most easily demonstrable are the effects of radium and roentgen rays may have a definitely injurious effect on germ cells.

After fertilization has occurred both the inherent qualities present in the zygote and the environment to which it is subjected determine both the normality of implantation and the embryonic and fetal development. Many embryos and fetuses succumb to unknown and nondemonstrable lethal factors. These ultimately may be shown to be due to inadequate germ plasm or be proved to be associated with vitamin, hormone, or other chemical influences during intrauterine environment.

The most important conditions which are known causes of death in fetal life are environmental. Malformations are an important cause of

*Read at a meeting of the Brooklyn Gynecological Society, Brooklyn, New York, February 4, 1938.

death in the embryonic and in the immediate postnatal period. If an abnormality is not of sufficient grade to cause death in the first few weeks of development, it is usually compatible with intrauterine fetal life and death is infrequent up to the time the fetus is born. Maternal disease of any type may affect the fetus either by interfering with normal nutrition or by a direct transference of toxic or infectious substances from the maternal to the fetal blood stream.

Abnormalities of the accessory fetal structures, amnion, placenta and cord, are largely environmental in origin. Premature separation of the placenta, which is often very injurious to the fetus, is frequently associated with some type of toxemia, and is definitely environmental. The cause of placenta previa is not definitely known, and it is possible that an abnormality either of the uterus or the ovum may be responsible. The most serious condition which affects the umbilical cord is its prolapse through the introitus. This rarely occurs if the membranes do not rupture until the presenting part is well engaged.

The period during which the fetus traverses the birth canal forms the most perilous interval of its entire intranatal or postnatal existence. This hazard is greatly increased if labor occurs before the fetus is mature; approximately ten times as many of the fetuses who are delivered prematurely die during delivery as of those who are delivered at term. In addition to prematurity the greatest birth hazards are those conditions which interfere with placental circulation, which cause trauma to the central nervous system or to the abdominal viscera, and which favor the ascent of infectious material from the lower genital tract into the amniotic sac or uterus. In the first group the fetuses die of anoxemia, in the second, of direct injury to the nerve centers in the brain or from visceral hemorrhage, in the third of acute infections which especially affect the lungs.

If the fetus survives the process of delivery it must still adjust itself to the rigors of an extrauterine existence; it must maintain its own body temperature, digest its own food, inhale its own oxygen, and eliminate its own waste products. It is suddenly exposed to the bacteria of a contaminated world. Fortunately in civilized countries the young infant is greatly protected from contact with harmful bacteria so that in the first few weeks of life the main causes of morbidity or mortality are the persistent effects of conditions affecting the fetus during the intrauterine period or during the establishment of extrauterine life. In later infancy bacterial infections cause a large proportion of the total deaths.

Any of the antenatal, intranatal, or postnatal factors which produce disorders of the fetus or infant may be carried into later infant, child, and even adult life to produce a handicapped existence or shortened life expectancy.

In the United States there has been a progressive reduction in the total death rate and a continual diminution in the infant mortality rate for many years. A close analysis of the latter, however, reveals that there has been little if any reduction in the neonatal death rate and practically none in the fetal death rate. In the United States mortality statistics for

the first year of life show a gradual decrease since 1915 (100 deaths per 1,000 live births in 1915, 56 per 1,000 births in 1935); the mortality subsequent to the first month of life shows a more marked decline (58 per 1,000 live births in 1915, 25 per 1,000 live births in 1935), but the mortality rate for the first day is almost a straight line from 1915 to 1935 (16 per 1,000 live births throughout the entire period), and the death rate during the first month shows only a very slight decrease (44 per 1,000 live births in 1915, 34 per 1,000 live births in 1935). The number of stillbirths has remained practically constant since figures on this subject have been collected by the census bureau (40 per 1,000 live births in 1922, 38 per 1,000 live births in 1934). While certain factors such as the more complete reporting, especially of premature births, may obscure some saving of life during this early period, the fact remains that only slight progress in a general reduction of the number of stillbirths or early infant deaths has been made.

It is difficult to compare statistics from any two countries or from any two institutions within the same country because of the variation in classification and of the age limits included. It would be of great help in evaluating methods used in treatment of the complications of pregnancy and labor if fetal and neonatal mortality could be accurately compared in different clinics. The only way to accomplish this is to have a uniform system adopted throughout the country.

The method found most valuable at the Chicago Lying-in Hospital is to use three criteria (menstrual age, fetal weight, and length) in determining the probable age of the fetus (Table I). All fetuses and infants

TABLE I. CRITERIA FOR ESTABLISHING AGE OF FETUS AND NEWBORN INFANT AT THE CHICAGO LYING-IN HOSPITAL*

I. Abortion	
	1. Less than 400 gm. in weight
	2. Less than 28 cm. in length
	3. Less than 22 weeks (missed abortions are excluded)
II. Premature	
A. Previable	
	1. From 400 to 999 gm. in weight
	2. From 28 cm. to 35 cm. in length
	3. From 22nd to the end of the 28th week
B. Viable	
	1. From 1000 to 2499 gm. in weight
	2. From 35.1 cm. to 47 cm. in length
	3. From 29th to the end of the 37th week
III. Term	
	1. From 2500 to 4499 gm. in weight
	2. From 47.1 cm. to 54 cm. in length
	3. From 38th to the end of the 42nd week
IV. Postmature	
	1. More than 4500 gm. in weight
	2. More than 54 cm. in length
	3. More than 42 weeks

*The infant is placed in the group in which two of the three criteria fall.

for which a stillbirth or death certificate is required by law are included in mortality reports. This includes many fetuses which have not yet

reached the period of viability and which cannot be expected to survive. The only justification for the use of "corrected mortality" figures is in those instances where an evaluation of a certain procedure makes it necessary to eliminate those cases in which the factor being investigated could not have played a contributing part. Citing "corrected mortality rates" as a hospital's actual mortality is never justified.

In the Chicago Lying-in Hospital from May 25, 1931, to Jan. 1, 1938, there were 17,728 deliveries, with 371 neonatal deaths and 402 stillbirths. The incidence of the various methods of delivery and the number of deaths occurring in each type are shown in Tables II and III.

TABLE II. INCIDENCE OF VARIOUS TYPES OF DELIVERY

	TOTAL NUMBER OF DELIVERIES	INCIDENCE PER CENT
Cephalic, natural	10,877	61.9
Cephalic, low forceps	3,995	22.5
Cephalic, midforceps	835	4.7
Breech	708	4.0
Cesarean section	1,041	5.8
Version and extraction	162	0.9
Miscellaneous	110	0.6

TABLE III. TYPE OF DELIVERY IN RELATION TO FETAL AND NEONATAL DEATHS

	TOTAL DELIVERIES	STILL-BIRTHS	NEONATAL DEATHS	TOTAL DEATHS	PER CENT
Cephalic, natural	10,877	170	174	344	3.0
Cephalic, low forceps	3,995	22	35	57	1.4
Cephalic, midforceps	835	22	20	42	5.0
Breech	708	61	56	117	16.5
Cesarean section	1,041	31	62	93	8.9
Version and extraction	162	35	23	58	34.5
Miscellaneous (Includes 59 craniotomies)	110	61	1	62	56.3

It is important to know the incidence of the various fetal age groups and the mortality rates of the different groups. Table IV shows that our total rate per thousand live born infants is 44, with a stillbirth rate of 23 and a neonatal death rate of 21. If one considers only the previable infants and fetuses, the corresponding rates are 988, 462, and 526, respectively. The corresponding rates for the viable prematures are 346, 165, and 181, respectively, and for term infants, they are 18, 10,

TABLE IV. MORTALITY RATES IN RELATION TO FETAL AGE AT TIME OF DELIVERY

	TOTAL BIRTHS	TOTAL NEONATAL MORTALITY	NEONATAL MORTALITY PER 1,000 BIRTHS	TOTAL STILL-BIRTHS	STILL-BIRTH MORTALITY PER 1,000 BIRTHS	TOTAL MORTALITY PER 1,000 BIRTHS
Term	16,529	133	8	189	10	18
Premature	1,043	189	181	170	165	346
Previable	93	49	526	43	462	988
Undetermined	63	---	---	---	---	---
Total	17,728	371	20	402	22	43

and 8. These comparisons are striking and indicate the importance of the problem of prematurity.

Investigation of the incidence of births of the different groups shows that the number of prematures is relatively small, as in over 93 per cent of the births the infants were at term, in 5.8 per cent they were viable prematures, and in only 0.5 per cent were they previable (Table V).

TABLE V. TOTAL DELIVERIES FROM MAY 25, 1931 TO JAN. 1, 1938

	TOTAL NUMBER OF DELIVERIES	PER CENT
Term	16,529	93.30
Premature	1,043	5.80
Previable	93	0.50
Unrecorded	63	0.38
Total	17,728	

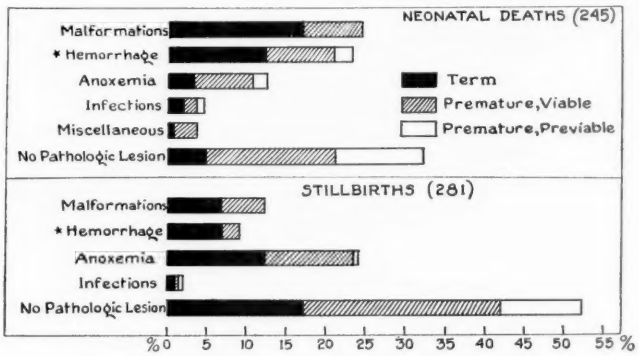
With a stillbirth rate of 36 and a neonatal rate of 34 for the United States, it is obvious that it is possible to secure an improvement in the fetal and neonatal mortality rates. This can be accomplished only by adequate maternal care. Inasmuch as fetal and neonatal deaths are largely due to conditions associated with childbirth, the problem is primarily an obstetric one. It is apparent that proper preconceptional and prenatal care would entirely eliminate fetal and neonatal disease due to syphilis. On the other hand it is quite obvious that with our present state of knowledge nothing can prevent disease and death due to malformations. Prematurity constitutes an extremely important problem. The only salvation for the previable group of premature infants is a prolongation of gestation. Whether or not gestation can be prolonged in these cases is a matter which must be determined in each individual case. Many previable births cannot be avoided but in some instances they can be, and in others the period of gestation can be prolonged to viability.

The methods of decreasing the number of deaths of premature infants are in the main two; first, the prolongation of gestation when it is feasible and safe; second, the provision of proper environmental conditions for the premature infant from the moment of birth. It must be recognized that in certain conditions such as the toxemias of pregnancy and nephritis, the prolongation of gestation is a hazard not only to the mother but also to the fetus and antenatal death may occur.

It is impossible to undertake to discuss in detail the procedures to be followed in treating the numerous complications of pregnancy and labor which would provide the greatest safety for the fetus as well as for the mother. Such analyses must be made, however, in relation to the causes of fetal and neonatal deaths and from them conclusions must be drawn as to which methods of treatment afford not only the maximum safety to the mother but also to the fetus.

Extensive studies of the causes of fetal and neonatal deaths are being made by the Department of Obstetrics and Gynecology of the University of Chicago. From 1931 to 1938 68 per cent (526) of all infants

stillborn or dying in the neonatal period at the Chicago Lying-in Hospital have been examined at autopsy. The major causes of death are shown in Chart 1. In live born infants dying in the neonatal period there are more premature infants who die without demonstrable pathologic lesions (27.6 per cent) than there are in any other single group. (Incomplete anatomic structure and physiologic function are largely responsible for these deaths.) The remaining causes of death in order of frequency are: malformations, 24.5 per cent; hemorrhage, 23.2 per



* *Hemorrhage includes only gross visceral and intracranial lesions*

Chart 1.—Causes of fetal and neonatal deaths (526 necropsies) in the Chicago Lying-in Hospital 1931 to 1938.

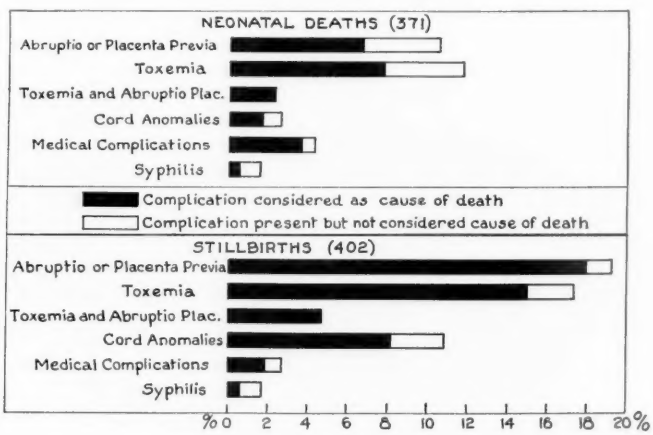


Chart 2.—Maternal complications associated with 773 fetal and neonatal deaths in the Chicago Lying-in Hospital 1931 to 1938.

cent; anoxemia, 12.2 per cent; infections, 4.4 per cent; miscellaneous, 3.6 per cent. In only 4.5 per cent of all term infants could no pathologic changes be shown. In stillborn infants the causes demonstrable by autopsy were anoxemia, 23.9 per cent; malformations, 12.4 per cent; hemorrhage, 9.2 per cent; infections, 1.9 per cent. Among the stillborn infants no pathologic changes (maceration is not included as a pathologic change) are found in a much higher percentage (52.6 per cent) of cases than among the infants dying in the neonatal period. However,

approximately half (48 per cent) of these cases showing no pathologic lesions were associated with maternal complications of which toxemia and maternal hemorrhage from placenta previa or premature separation of the placenta were the most common.

In the entire group of 773 stillbirths and neonatal deaths there was an associated complication of pregnancy or labor (exclusive of difficult or operative delivery) in 33 per cent of the live born and in 57 per cent of the stillborn infants, or in 45 per cent when both groups are considered together. In only 32 per cent, however, could the complication be considered as the probable cause of death. In the other 13 per cent definite pathologic lesions such as intracranial hemorrhage, infections, malformations, etc., were believed to take precedence over the complication as lethal factors. Chart 2 shows the incidence of the different complications in association with both fetal and neonatal deaths. It is to be noted that in only 13 of the entire group was the maternal Wassermann reaction positive and in only 4 of the infants was death believed due to syphilis.

It is evident that the persistently high fetal and neonatal mortality rates and the morbidity which is undoubtedly associated with these stationary rates present a challenge which must be met by the obstetricians. It can be met only through providing painstaking and intelligent preconceptional, prenatal, intranatal, and postnatal observation and advice. If generally and properly applied our present knowledge is sufficient to cause a gradual reduction in the fetal and neonatal morbidity and mortality to a minimum. With increasing knowledge and improvement in its application, such a minimum should in the future be further reduced by greater knowledge and its more intensive application.

SUMMARY

1. Fetal and neonatal disease and death may result from hereditary factors.

2. Environmental factors may operate upon the germ cells, embryo, and fetus prior to and during pregnancy.

3. The environmental factors occurring during the onset and course of labor are extremely important in the causation of fetal and neonatal disease and death.

4. Control of postnatal environment is especially important in preventing deaths of premature infants.

5. It is obvious from studies of results obtained in certain areas that the unchanging level of fetal and neonatal deaths can be made to decline by providing proper care for the mother, fetus and newborn infant.

INDUCED HYPERGLYCEMIA AT DELIVERY

Its Effect and Clinical Application

Rose C. Ketteringham, B.S., Cleveland, Ohio, and Bruce R. Austin, M.D., Pittsburgh, Pa.

(From the Laboratory of the Maternity Hospital, Cleveland, Ohio)

IN ORDER to fortify a patient after a prolonged labor, it has been the custom at the Maternity Hospital to administer 10 per cent dextrose intravenously just prior to delivery. During our study of the blood sugar in normal labor,[1] it occurred to one of us that the high blood sugar values thus effected in mother and newborn might approximate the levels found in diabetic patients and their infants.

The case which suggested this study was that of a primipara having a first stage of forty-eight hours' duration. She was given 500 c.c. of 10 per cent dextrose one hour and ten minutes before delivery. Immediately before the administration of dextrose her blood sugar was 122 mg. per 100 c.c.; at the moment of delivery, it was 380.4, and that of the baby was 338.8 six minutes after birth. At twelve hours of age this newborn baby had a blood sugar of 81.6, nothing having been taken by mouth.

Blood sugar values on ten cases of normal newborn infants three to six hours of age have been previously reported;[1] the values ranged from 56.9 to 79.1 mg. per 100 c.c., the mean being 66.8. It is evident that in newborn babies the slightly elevated values of birth drop to the normal infant range within a short time.

Preliminary study on three patients showed that the administration of 500 c.c. of 10 per cent dextrose intravenously within one hour of delivery produced a blood sugar level of 400 to 500 mg. per 100 c.c. immediately following the injection. Maternal values of 220, 261, and 350 mg. per 100 c.c. at delivery in these three cases seemed to be dependent upon the length of time elapsing between the injection and delivery, since the dextrose was rapidly removed from the circulating blood. Values on the infants ten to twelve minutes after birth were found to be 100 to 150 mg. per 100 c.c. higher than their respective mothers prior to the injection, indicating diffusion of the glucose to the fetus through the placenta. Within three to four hours after birth, the blood sugar values had fallen to the normal postpartum maternal and infant ranges. The data on these preliminary cases are presented in Table I.

Table I

MATERNAL BLOOD SUGAR 1 MIN. BEFORE 10% DEXTROSE	MATERNAL BLOOD SUGAR 1 MIN. AFTER 10% DEXTROSE	MINUTES BETWEEN INJECTION AND DELIVERY	MATERNAL BLOOD SUGAR AT DELIVERY	NEWBORN BLOOD SUGAR 10-12 MIN. AFTER BIRTH	MATERNAL BLOOD SUGAR 3 HR. AFTER DELIVERY	NEWBORN BLOOD SUGAR 3-4 HR. AFTER BIRTH
91.1	452.9	41	220.0	202.4		71.1
98.1	437.0	18	350.0	245.5	106.9	64.5
125.8	421.0	50	261.0	261.6	131.9	75.2

With these preliminary figures in mind, the following study was planned:

1. To administer during the second stage of labor approximately 500 c.c. of 10 per cent dextrose (50 gm.) intravenously, at a rate of 30 to 40 c.c. per minute, obtaining blood sugar values before and after such administration, samples to be taken from the hand on the side of the body opposite the site of injection.

2. To follow by hourly estimations after delivery the fall of the blood sugar in mother and newborn for the first four hours, this period being found sufficient through preliminary work.

3. To study, as a control group, several normal mothers and newborn infants by the same technique, but without having administered dextrose.

A search of the literature has revealed no similar study. Apparently very little work has been done on the blood sugar values in newborn infants. Holman and Mathieu[2] report a case of toxemia seen in consultation in which 300 c.c. of 25 per cent dextrose (75 gm.) was administered fifteen minutes prior to delivery. The blood sugar of this patient at delivery was 424 mg. per 100 c.c., and that of her infant (taken from the maternal end of the cord) was 439 mg. per 100 c.c. Apparently they did not follow the blood sugar of the infant after birth.

In a study such as this the validity of the conclusions is influenced by a number of factors. We have, therefore, attempted to hold variations in technique to a minimum. It is obvious that the concentration of the blood sugar may vary in different parts of the body following injection of large amounts of hypertonic dextrose, especially when that body is simultaneously eliminating excess glucose from the blood stream. For this reason, we feel that studies of this nature are best performed on

TABLE II. DATA ON MEDICATION AND DELIVERY

CASE	PARA	MEDICATION	BLOOD SUGAR AT DELIVERY		PRESENTATION AND DELIVERY
			MATERNAL	INFANT	
Normal Controls					
C 1	i	M & S* × 6	160.9	147.7	Breech extraction
C 2	i	M & S × 5	103.7	93.8	Podalic version, breech extraction
C 3	i	M & S × 3	170.1	121.8	R.O.A., Modified Scanzoni, low midforceps
C 4	i	None	135.5	87.0	L.O.A., Low forceps
Patients Having 500 c.c. 10 per cent Dextrose					
G 1	i	Sod. amytal gr. ix	368.5	192.3	R.O.T. to R.O.A., Low forceps
G 2	i	M & S × 3	328.8	240.6	R.O.A., Low forceps
G 3	i	M & S × 2	411.7	365.9	Low midforceps, axis traction
G 4	iv	Sod. amytal gr. ix	351.6	199.1	R.S.P., Breech extraction } Twins
				201.2	R.S.P., Breech extraction }
G 5	i	M & S × 4	277.0	226.6	R.O.A., Midforceps
G 6	i	M & S × 3	269.9	237.6	R.O.A., Low midforceps
G 7	i	M & S × 4	325.0	267.8	R.O.A., Low midforceps

*Morphine sulphate and scopolamine hydrobromide. All patients had ether analgesia and ether anesthesia.

blood samples taken from corresponding parts of the body in mother and infant. We have consequently been limited to micromethods using capillary blood, since this permits repeated analysis on newborn infant and mother without the complications accompanying venipuncture.

METHOD

All blood sugar estimations were made by the same person, using the Jeghers-Myers[3] modification of the Folin-Malmros ferricyanide micromethod.[4] The occurrence of high blood sugar values necessitated determination on half portions of filtrate where such values were expected as suggested by Jeghers and Myers. A

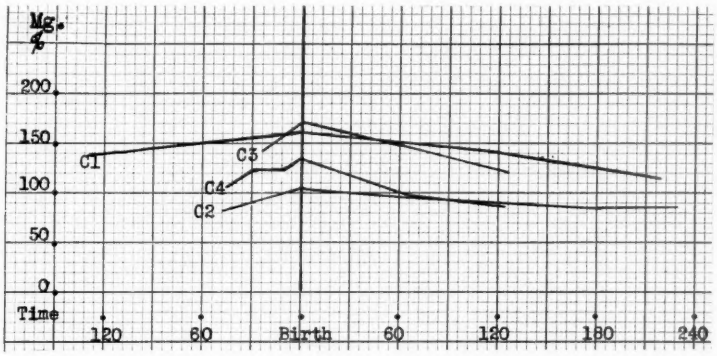


Fig. 1.—Fall in blood sugar following delivery in maternal controls.

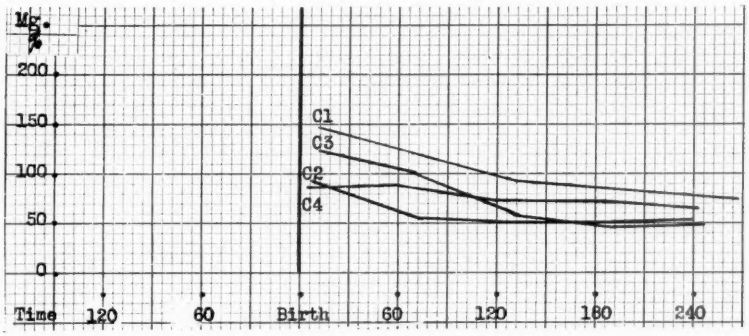


Fig. 2.—Fall in blood sugar following delivery in newborn controls.

series of standards equivalent to 70, 105, 140, 175, 210 and 280 mg. per 100 c.c. was used. When blood sugars in the range of 175 to 275 mg. per 100 c.c. were anticipated, both full and half-portions of filtrate were used. For higher values, half-portions were uniformly used and the results doubled. All colorimetric readings were made through a picric acid light filter. The final curves presented are the result of selection of the figures deemed most accurate in the range above 200 mg.; below this range no selection has been exercised. Since practically all of the infant determinations, more than 50 per cent of the maternal determinations, and all the control determinations are below 200 mg. per 100 c.c., it is evident that the curves are based for the most part on unselected data.

Delivery in normal controls and in patients having dextrose was effected by prophylactic forceps or breech extraction, and was preceded by analgesia suitable to the case. Delivery care at the Maternity Hospital has been previously summarized.[1] Data on medication and delivery are presented in Table II.

ANALYSIS OF DATA

Figs. 1 and 2 show the fall in blood sugar following delivery in control mothers and infants, respectively. All the maternal and infant blood sugar values at delivery are within the normal delivery range, and there is a gradual fall to normal postpartum and newborn levels within three to four hours.

In Fig. 3 the curves for mothers having 500 c.c. of 10 per cent dextrose are summarized. Of the 7 patients, 5 attained blood sugar levels of 400 to 500 mg. per 100 c.c. Nothing in the case histories of the other two indicated the reason for the

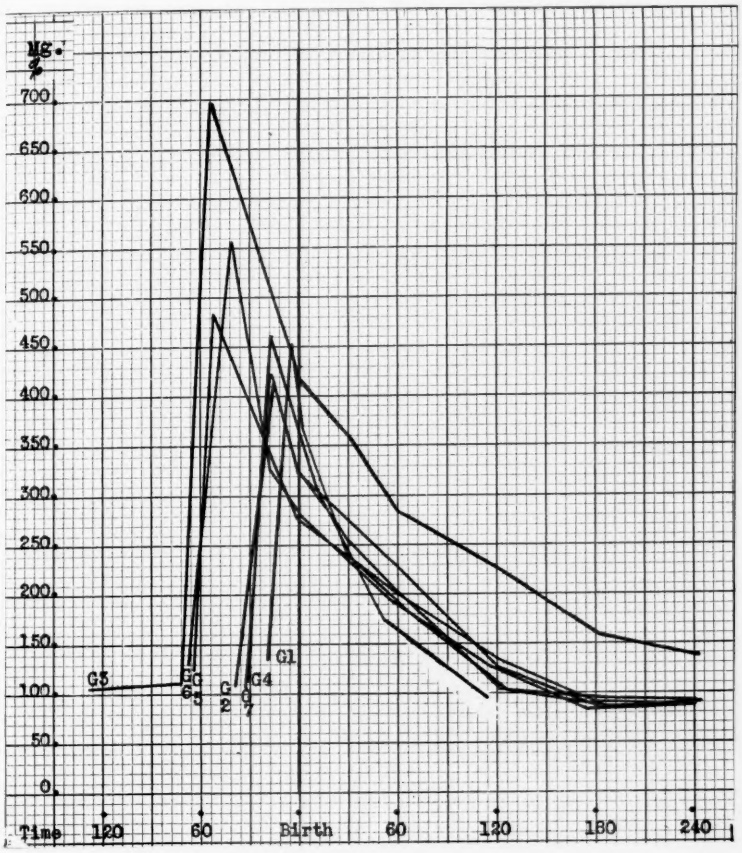


Fig. 3.—Fall in blood sugar in patients having 500 c.c. of 10 per cent dextrose.

rise to 556 to 698, respectively. Titus and Lightbody investigating the therapeutic dose of intravenous dextrose found that a small number of otherwise normal individuals respond to injections of dextrose with higher than average blood sugar values. It seems reasonable to conclude, therefore, that Case G 6 is of this type, since this curve does not show pancreatic impairment. Case G 3 might possibly be interpreted as showing slight pancreatic impairment, although detailed studies were not made. With the exception of this latter case, the blood sugar values at delivery are seen to be directly dependent upon the time elapsing between the end of administration and the moment of delivery, i.e., the closer to delivery the dextrose is administered, the higher the blood sugar at delivery. Four patients who received dextrose within thirty minutes of delivery had blood sugar values at delivery ranging from 325 to 368.5, with a mean of 341. Two others receiving dextrose more than thirty minutes before delivery had blood sugar values at delivery of 277 and 269.9.

Six of the 7 patients had blood sugar values within the normal post-partum range three to four hours following delivery.

In Fig. 4 are summarized the curves on 8 infants of mothers receiving dextrose. One infant (that of Case G 3) presented a blood sugar at delivery of 365.9, and throughout the first three hours remained higher than the group, dropping to 45.9

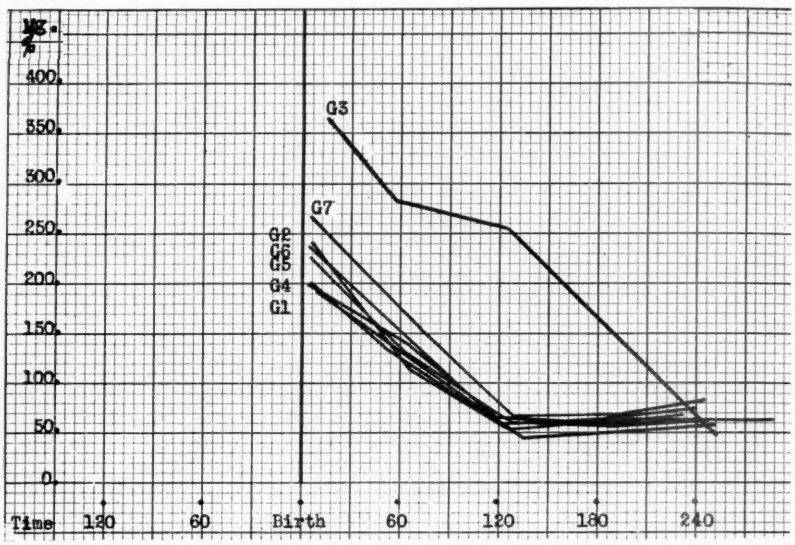


Fig. 4.—Fall in blood sugar on newborn infants of mothers receiving dextrose.

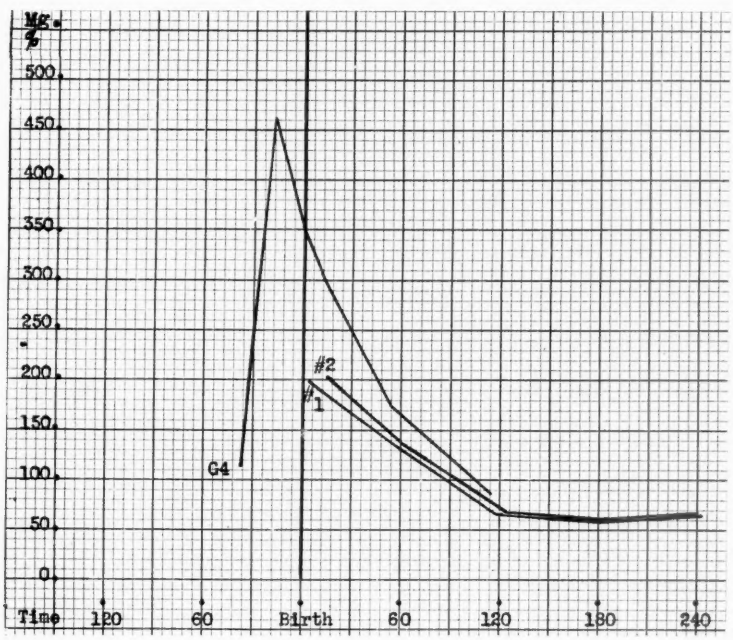


Fig. 5.—Relationship between blood sugar values of mother and her twin newborn infants when 500 c.c. of 10 per cent dextrose was administered intravenously. (Case G 4.)

mg. per 100 c.c. at four hours. The other 7 infants studied showed blood sugar levels at delivery ranging from 192.3 to 267.8 with a mean of 223.6. Identical twins had blood sugar values of 199.1 and 201.2 at delivery, and values throughout the next four hours remained within 3 mg. of each other. One hour following delivery blood sugar values on these 7 infants had dropped to a range of 110 to 140. At two hours, the values ranged from 45 to 65 mg. per 100 c.c. At four hours, a slight rise to a range of 55 to 80 mg. per 100 c.c. was uniformly evident.

To show the relationship between a series of determinations on mother and infant, we present in Fig. 5 the reaction of Case G 4 and her twin infants to 500 c.c. of 10 per cent dextrose administered intravenously.

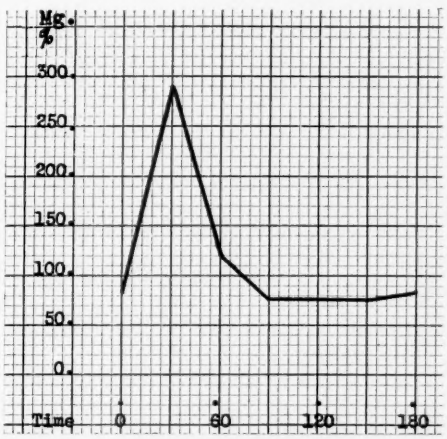


Fig. 6.—Blood sugar of normal infants after intravenous administration of 10 c.c. per pound of body weight of a 10 per cent solution of dextrose. (*Tisdall, Drake and Brown:* Am. J. Dis. Child. 30: 675, 1925.)

From a study of the data presented here, we conclude that pancreatic activity at birth is such that the blood sugar values of normal control infants and of those receiving dextrose reach normal infant levels within four hours. The slight but apparently characteristic rise occurring between the second and fourth hour in the infants receiving dextrose suggests the hypoglycemic reaction demonstrated by Tisdall, Drake and Brown[6] in slightly older infants after intravenous administration of dextrose. In their study, 10 c.c. of 10 per cent dextrose per pound of body weight caused a rise in blood sugar to 290 mg. per 100 c.c., followed in 90 to 120 minutes by a typical hypoglycemic curve, unaccompanied by clinical signs. For comparison, we reproduce the curve they obtained as Fig. 6.

The most striking feature of this work is the rapidity with which the normal infant, whatever its blood sugar value at birth, assumes the normal value for newborn infants. Factors influencing the blood sugar of the mother must be considered in the interpretation of estimations made during the first few hours of life. The unusual importance of the time element in a series of rapidly decreasing blood sugar values becomes apparent when the curves presented in Fig. 4 are carefully studied.

In turning to the clinical application of this work we have shown that it is possible to fortify not only the mother but also the premature infant, or the infant of the toxemic patient by administration of dextrose.

However, the effects of the procedure last only a few hours. In addition to its temporary nature, promiscuous use of this technique seems unjustified inasmuch as it may add considerable strain to the newborn infant already coping with the problem of adjustment to a new environment. The mother could be as adequately strengthened and any strain on the newborn infant prevented by administration earlier in labor at a physiologic rate, provided the patient's condition be such that this additional fluid load would be harmless.

We believe the clinical application of this study is to be found in the treatment of the infants of diabetic mothers. The blood sugar curves in Fig. 4 show that the pancreas of the newborn infant is as susceptible to stimulation as that of slightly older infants. These curves coincide remarkably with the work presented by Tisdall, Drake and Brown[6] on infants from one to twelve months of age, having 10 c.c. of 10 per cent dextrose per pound of body weight. Our experience with hypoglycemia in the 7 infants studied duplicates that of these workers, who showed that hypoglycemia may exist in infants without clinical signs. It seems, therefore, in caring for the newborn infants of diabetic patients that to delay until the onset of clinical signs of hypoglycemia to institute glucose therapy is to invite unnecessary, and possibly fatal, hypoglycemia. Repeated determinations of blood sugar to estimate the approximate time when hypoglycemia may be expected to occur and to guide the glucose therapy may not be practical in all cases.

The alternative to frequent blood sugar determinations is parenteral administration of dextrose at intervals. Our work and that of Tisdall, Drake and Brown[6] provides a basis for dosage and interval in such therapy. The dosage should be sufficient to put the blood sugar definitely above the hypoglycemic level, and to keep it raised for a length of time. Some workers[7] have advocated 5 to 10 c.c. of 10 per cent dextrose, which seems in the light of our work to be inadequate. Tisdall, Drake and Brown[6] demonstrated that subcutaneous administration of 5 per cent dextrose (10 c.c. per pound of body weight) caused a rise of 30 mg. per 100 c.c. in the blood sugar, while 10 and 15 per cent solutions in the same ratio caused a rise of 130 mg. per 100 c.c. In their cases, about 2 per cent of the dextrose was excreted in the urine.

Since it seems wise to avoid placing undue strain on the pancreas and liver of the infant of the diabetic patient, we suggest that the dosage of dextrose used be intermediate between these two viewpoints, namely, 10 c.c. of a 10 per cent solution per kilogram of body weight, administered subcutaneously. This amount will sustain the blood sugar for a period of two to three hours and the effects of the therapy will be evident for a longer time. The interval between administration of dextrose should be at least three hours, and preferably two to three times this long, to allow for the normal cycle of absorption, hyperglycemia, fall, hypoglycemia, and rise to fasting level. Failure to observe this time interval may result in a clinical picture obscured by pancreatic fatigue due to the constant stimulation of this organ. As soon as possible, oral feeding of karo water and formula should be substituted for parenteral administration of dextrose.

In addition to the administration of dextrose in sufficient dosage, and at proper intervals, we believe all babies of diabetic mothers should be treated as premature, regardless of weight. The constant nursing care required by prematures corresponds to that needed by the infant of the diabetic patient; it can be most simply and easily obtained by putting the infant on routine premature care. Only in this way can these newborn infants be guarded from infection, maintained at the proper temperature, and regulated in feedings without disruption of the hospital and nursery routine.

The cooperation of the laboratory service is essential. It has been found practical at the Maternity Hospital to assign a single technician to the work on diabetic patients and their infants, so that the routine of the delivery room and laboratory may proceed without disruption. When a diabetic case is anticipated, reagents and glassware are kept in readiness, and the technician is prepared to render prompt reports on urine and blood sugars.

CONCLUSIONS

1. Dextrose administered intravenously during the second stage of labor causes a definite hyperglycemia in mothers at delivery and in their infants at birth.

2. Maternal blood sugar values reach 400 to 500 mg. per 100 c.c. just after dextrose is administered and fall to normal post-partum levels three to four hours after delivery.

3. The closer to delivery dextrose is administered the higher the blood sugar values at delivery.

4. The blood sugar of newborn infants whose mothers had dextrose ranged from 192 to 267 mg. per 100 c.c. with a mean of 223.

5. There is a rapid fall in the blood sugar values of these newborn infants, resulting in a hypoglycemia which may be as low as 45 mg. per 100 c.c. followed by a slight characteristic rise.

6. Clinical application of this study is to be found in the care of newborn infants of diabetic individuals. The following are suggestions for care:

RECOMMENDATIONS FOR CARE OF NEWBORN INFANTS OF DIABETIC PATIENTS

1. Make blood sugar determination on capillary blood as soon as possible after birth, and as often as practical at intervals for the first few hours.

2. At the first indication (by laboratory findings) of hypoglycemia, 10 per cent dextrose should be administered subcutaneously in a dosage of 10 c.c. per kilogram of body weight, repeated as necessary.

3. Intervals between administration of dextrose should be at least three hours, and preferably longer.

4. Oral feedings should be instituted as soon as possible.

5. Newborn infants of diabetic patients should be placed on routine premature care, regardless of weight, since this is the most efficient way of giving these babies the constant nursing care they require.

6. Cooperation of medical, obstetrical and laboratory services is the best way of meeting the complications of diabetics and their infants.

We wish to take this opportunity to express our appreciation to Dr. Arthur H. Bill for permitting this study, and to the resident staff of the Maternity Hospital for cooperation in its execution.

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SO-CALLED LUTEIN CELL TUMORS*

Otto Saphir, M.D., Chicago, Ill.

(From the Department of Pathology of the Nelson Morris Institute, Michael Reese Hospital)

EXCLUDING the basophilic adenoma of the pituitary gland which may or may not produce Cushing's syndrome and signs of masculinization, there are two or perhaps three ovarian tumors and a suprarenal cortical tumor which produce masculinization. One of these is the arrhenoblastoma. My discussion shall be confined to the suprarenal cortical tumor and to an ovarian tumor which may be identical with the suprarenal tumor or which may be a lutein cell tumor.

The suprarenal tumors are intriguing. It seems that only malignant tumors arising in the suprarenal cortex are linked with changes in the secondary sex characteristics. If these tumors occur before puberty, they produce in both sexes precocious development and virilism (Meyer and Frumess[1]). Such a tumor came to our observation. The patient, a thirteen-year-old girl, presented typical pubertas praecox with virilism and hirsutism. At the autopsy, a carcinoma of the suprarenal cortex was found with metastases to the retroperitoneal lymph nodes and to the liver. In the mature female this tumor may produce masculinization (Cahill and co-workers[2]). Such an observation was also made by us in a 40-year-old female who presented a malignant tumor in the cortex of both suprarenals. A chromophobe adenoma of the hypophysis, perhaps an incidental finding, was also found at autopsy. In the adult male carcinoma of the suprarenal gland may rarely produce evidence of feminization (Lisser[3]). However, there are a number of instances of carcinoma of the suprarenal cortex in both sexes, which have produced no changes in the secondary sex characteristics.[2] Two such instances were also observed by us. In one of these, a kidney tumor was diagnosed clinically. In both the autopsy revealed a carcinoma arising in the suprarenal cortex.

*Presented before the Chicago Gynecological Society, October 21, 1938, as part of a Symposium on ovarian tumors.

This short survey reveals that there is a malignant tumor arising in the suprarenal cortex, a carcinoma, also called hypernephroma, which is closely linked with changes in secondary sex characteristics; most commonly pubertas praecox and virilism, if occurring before puberty, or masculinization in the adult female.

There are tumors called hypernephromas or Grawitz tumors frequently found in the kidney which are said to arise from misplaced suprarenal cortical structures. These tumors are usually bright yellow, show secondary degenerative changes and hemorrhage, and grossly and microscopically resemble those arising in the suprarenal cortex. As a matter of fact, most malignant kidney tumors are of this type. The conception of the suprarenal origin of these tumors is based upon the belief that occasionally suprarenal rests are found in the kidney, that the cells of these tumors closely resemble those seen in the suprarenal cortex and that this tumor is, as a rule, either encapsulated or seemingly well separated from the adjacent kidney structures. Not wanting to go into a discussion of what is in favor and what is against the assumption of the suprarenal origin of these kidney tumors (Saphir[4]), it may suffice to state that the mere resemblance of cells does by no means indicate a genetic relationship. This also holds for a number of so-called suprarenal rests which are said to occur quite often in the kidney. Many of these supposed suprarenal cortical rests are mere adenomas with clear cells arising from kidney tubules. The more modern conception of the so-called hypernephromas of the kidney indicates that they are carcinoma with clear cells arising, not from misplaced suprarenal cortical cells, but from similar structures such as the above-mentioned adenomas. The term hypernephroid carcinoma is merely used to denote the resemblance of these to suprarenal tumors. In favor of this conception is also the fact that, whereas the malignant cortical suprarenal tumors are in a number of instances linked with inner secretory disturbances, there is, as far as I am aware, not a single undisputed case on record where a so-called hypernephroma of the kidney, the supposed misplaced suprarenal tumor, has produced changes referable to secondary sex characteristics.

Bright yellow tumors, grossly resembling suprarenal cortical tumors and so-called hypernephromas of the kidney, also occur, though rarely, in the ovary. Descriptions of these tumors and references to other published cases are given by Glynn[5] and more recently by Schiller,[6] and Novak and Wallis.[7] These ovarian tumors are associated with masculinization and are much rarer than arrhenoblastomas. Grossly and microscopically they resemble suprarenal cortical tumors and also the so-called hypernephromas of the kidney. Like some suprarenal tumors, they produce masculinization, which may disappear after their surgical removal. On theoretical grounds and also from the morphologic and physiologic point of view, it is conceivable that these tumors actually arise from suprarenal rests. There are perhaps only three objections to this point of view. While suprarenal rests are described within the broad ligament and close to the ovary and also within the hilus of the

ovary, these rests, according to Novak and Wallis[7] are as a rule not found within the ovary itself. I myself have seen extremely few structures in the ovary which could be interpreted as misplaced suprarenal cortical tissue (Reis and Saphir[8]). This would indicate that a yellow

Fig. 1.

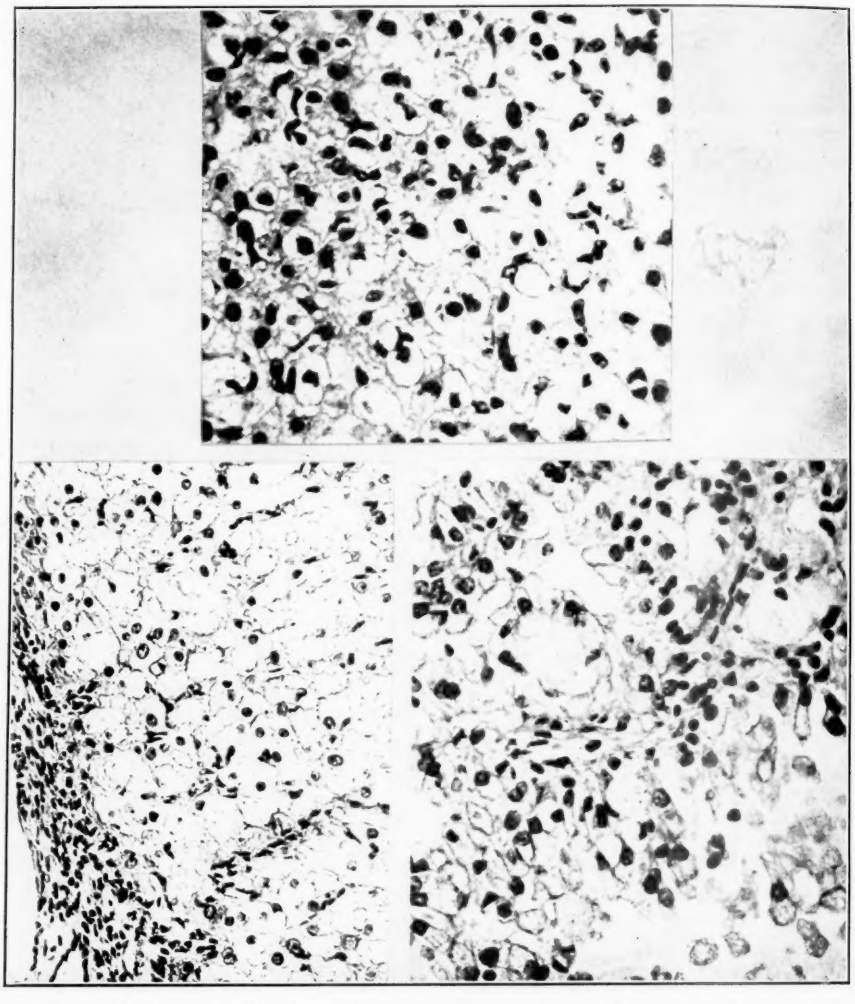

Fig. 2.

Fig. 3.

Fig. 1.—Section of yellow tumor in the ovary. (Lutein cell blastoma? Hypernephroma?) (Note the clear cells.) Iron-hematoxylin-eosin preparation; ×275.

Fig. 2.—Section of corpus luteum. (Note the resemblance of these cells to those of Figs. 1 and 3.) Iron-hematoxylin-eosin preparation; ×275.

Fig. 3.—Hypernephroid carcinoma of the kidney. (Note the resemblance of the tumor cells to cells in Figs. 1 and 2.) Hematoxylin-eosin preparation; ×275.

tumor, arising outside but close to the ovary, and which had produced changes in the secondary sex characteristics, may perhaps be interpreted as a tumor having arisen from misplaced suprarenal cortical structures. Such a tumor, of course, secondarily may invade the ovary itself. It seems extremely unlikely that a tumor of this type should arise within the ovary itself, because of the extreme rarity and doubtful occurrence

of suprarenal rests within the ovary as compared to the relative frequency of their occurrence in other locations. Another possible objection to the suprarenal origin of these ovarian tumors would be invalidated if it were actually proved that so-called hypernephromas of the kidney to which they are linked are not suprarenal tumors but true kidney tumors. If it were true that these tumors are suprarenal tumors misplaced within the kidney, just like these ovarian tumors, it would be difficult to understand why the latter should produce changes in the secondary sex characteristics and not the former. Still another argument against the assumption of the suprarenal origin of these ovarian tumors is the fact that every normal ovary normally contains cells and structures which also resemble the cells of which this yellow ovarian tumor consists, and which are possible sources of origin of this tumor. These cells and structures are lutein cells and corpora lutea, respectively. So it would seem probable that the so-called hypernephroma of the ovary is perhaps not a misplaced suprarenal cortical tumor, but a true ovarian tumor, a lutein-cell blastoma. Theoretically a tumor arising from lutein cells may give rise to masculinization because of its progesterone content. Whether such a lutein cell blastoma actually arises from corpus luteum cells or from granulosa cells which are in the process of luteinization is also very difficult to decide.

Because both the hypernephroma and lutein cell blastoma grossly and microscopically look very much alike it would seem next to impossible to differentiate these tumors histologically. Though Masson[9] claims that the latter shows a reticulum which is absent in the former, there are hypernephromas in which a reticulum is demonstrable. Since both tumors look alike, grossly and microscopically, and since both may give rise to masculinization, it is extremely likely that there is only one bright yellow tumor, arising within the ovary, which histologically consists of clear cells, resembling those seen in the suprarenal cortex and in the hypernephroid carcinomas of the kidney, and also in the corpus luteum. This tumor is closely linked to masculinization. Everything else being equal, and if one does not want to accept Cohnheim's theory without reservation, it seems safer to explain the origin of a tumor as arising from elements of the organ in question rather than from embryologically misplaced structures in that particular organ.

In the literature, there is some discussion as to the origin of these yellow ovarian tumors. In passing it may be mentioned that Schiller stated that there are only four cases which may belong to a group of masculinizing ovarian tumors and which consist predominantly of cells which store lipoids. These are the cases of Cosacesco and others,[10] Sellheim,[11] and Novak and Wallis.[7] However, Schiller[6] classified these tumors as hypernephromas and not as lutein cell blastomas, principally because they are well circumscribed and the cells in these yellow tumors are well defined, whereas granulosa-lutein cells show intercellular bridges. Further the absence of follicles in these tumors, the presence of polycythemia, hypertension and hyperglycosuria in these patients further substantiated his belief. It may be mentioned that because the

tumor appears to be well circumscribed does not necessarily indicate an origin from misplaced structures since the so-called hypernephroid carcinoma of the kidney, which probably arises from kidney structures, is also seemingly well circumscribed. The tumor which was described by Reis and myself[8] and which undoubtedly falls into this group consisted of cells which were well separated from one another and did not reveal intercellular bridges. However, this patient showed normal blood sugar and had neither polycythemia nor hypertension.

Physiologic studies with extracts of these ovarian tumors have not been made as far as I am aware, probably because of their rarity. In the future, however, it may be possible perhaps to prove the origin of these tumors and to determine whether they are lutein cell blastomas or hypernephromas. It should be possible to extract progesterone from these tumors, provided they are lutein cell blastomas, and adrenosterone, if they are true suprarenal cortical tumors. However, the differentiation between progesterone and adrenosterone may be difficult. Qualitatively there is very little difference between them (Koch[12]); quantitatively they may be differentiated. If the activity of testosterone is taken as 100 per cent the physiologic activity of adrenosterone is considered 40 per cent and that of allo-pregnandiol and pregnane, metabolic products of progesterone, as 20 to 35 per cent. Also Kendall, Wintersteiner, and Reichenstein according to Koch[13] have prepared an oxidation product from an adrenal cortical principle which is found to be one-sixth to one-fourth as active as androsterone in the capon test. So it may be possible in the future to determine the potency of extracts of these ovarian tumors and hence differentiate them by their biologic assay.

There is perhaps another way of definitely deciding whether these ovarian tumors are hypernephromas or lutein cell blastomas, and this should be tried in every instance of a yellow ovarian tumor giving rise to masculinization. Very recent experiments performed by Anderson, Haymaker and Joseph[14] have shown that the life of adrenalectomized rats may be prolonged beyond the survival periods of untreated controls if such rats are injected with benzene extracts of blood taken from patients who had the hyperadrenalo-cortical syndrome (Cushing's syndrome); the urine of one of these patients showed a similar effect. If this is true for patients with hyperadrenalo-cortical syndrome, it may very well hold for patients who have suprarenal cortical tumors, either within the suprarenal or arising in misplaced suprarenal cortical tissues. This seems evident because of the physiologic changes in all these patients. This observation of Anderson and her co-workers may be significant, in regard to the differentiation between lutein cell blastomas and hypernephromas. If benzene extracts of blood from patients suffering from such an ovarian tumor prolong life of adrenalectomized rats, it would seem that such an ovarian tumor is a hypernephroma. If this test should prove negative and on operation a yellow ovarian tumor is found, similar to the one here described, it is much more likely that this tumor then must be classified as lutein cell blastoma. Naturally this would only hold true if, first, it could be shown that progesterone

does not prolong the survival period of adrenalectomized rats, and, second, that adrenosterone, respectively cortin, is not present in corpus luteum tumors.

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DISCUSSION ON PAPERS OF DRS. KANTER, SAPHIR AND GREENHILL

DR. WALTER SCHILLER.—When one analyzes the term lutein cells from the point of view of histology, one must realize that these cells are not an entity by themselves. Such cells were not originally lutein cells but started out either as granulosa or theca cells and became luteinized secondarily; it is only then that they deserve the name lutein cells. If a luteoma is described as consisting of lutein cells there must be either theca lutein or granulosa lutein cells. They cannot be theca lutein cells, because these are a connective tissue type, while the cells of luteomas are epithelial cells. The tumor composed of theca lutein cells is the well-known xanthofibroma. In case the luteoma cells are granulosa lutein cells, two possibilities for their development are present: (a) first luteinization and second neoplastic proliferation. This means that the granulosa cell is first luteinized just as in a corpus luteum and then pathologically proliferating as in a new growth. This is not likely, since the cells of the luteinized corpus luteum are too differentiated and specialized to maintain this power of physiologic proliferation, and certainly not the capacity of neoplastic proliferation, and (b) first a neoplasm arises from granulosa cells which secondarily becomes luteinized. Such cases have been described but these tumors present a very slight degree of luteinization, not to be compared with loading of fat of the luteoma cells. Transitional phases from the poorly luteinized granulosa cell tumor to the fat-laden luteoma would prove that the latter is derived from the former but these have not been found to date. There are valid morphologic reasons against the origin of luteomas from granulosa lutein cells. Granulosa arises from mesenchyme and shows its mesenchymatous origin as long as it is not luteinized by syncytial connections of the protoplasm of the single cells which do not have distinct cell boundaries. When reaching a higher differentiation by luteinization, the single cells are still connected by fibers which pass from the protoplasm of one cell to the protoplasm of the neighboring cells. The luteinized granulosa cells do not have sharply demarcated cell boundaries, whereas the cells of the luteomas show the typical epithelial cell borders and no cell connecting fibers. In examining the luteomas for areas in which the cells do not contain fat, I have found such areas in almost all luteomas. The cells of such areas never prove the syncytial character of unluteinized granulosa cells but correspond morphologically very closely to the sharply demarcated polyhedral cells in areas of the adrenal cortex or of cortical hypernephromas in which the cells have not undergone fat storage.

DR. R. R. GREENE.—I am speaking purely as a physiologist; Dr. Schiller intimated that thecomas should not be considered as derived from the ovary, as they produce male sex hormone. I beg to state that the ovary does produce male sex hormone. Dr. Papanicolaou many years ago proved in guinea pigs that ovaries stimulated with anterior pituitary-like hormone could produce androgenic substance. In those ovaries there was a marked overgrowth of what he called interstitial tissue

which is derived from luteinized theca cells. Recently we did the same work in the rat and we got a marked growth of the clitoris. Dr. Hill about two years ago transplanted ovaries to the ears in the male rat from which the testes had been removed, and those ovaries produced sufficient androgen to keep the prostate and seminal vesicles in a normal state. To say that the ovary produces androgen does not mean it is testosterone; there are a number of androgens. As reported recently in some work at the University of Chicago and confirmed by us, progesterone in excess amounts is an androgenic substance in that it will maintain the prostate in castrated animals in normal condition. Also, progesterone given in excessive amounts to immature rats will make the clitoris grow just as with testosterone.

Dr. Kanter mentioned that there was decreased sodium in the blood and urine and said it was hard to explain. It is hard to explain how the blood sodium would be decreased but the urine sodium would be decreased due to the "sodium retaining effect of the high concentration of sex hormone."

Dr. Saphir said that testosterone is found in adrenal tumors. I believe that is not quite true. Adrenosterone has been found in adrenal tumors. This is not testosterone which is the male hormone as found in the testes. He also said that it is chemically impossible to differentiate between progesterone and testosterone. The chemical differentiation between the two with colorimetric methods or actual chemical test tube tests is not particularly difficult. The differentiation is comparatively easy in biologic assays.

Dr. Saphir also discussed the recent work of Anderson at the University of California, in which she extracted blood and urine from patients with Cushing's syndrome which she believes to be due to hyperadrenal-cortical changes, and found these extracts would maintain life in adrenalectomized rats. These patients did not show any virilizing changes; these patients did not have androgenic adrenal cortical tumors. It is difficult, then, to see how this test would be of value in differentiating ovarian and adrenal tumors.

DR. SAPHIR (closing).—The recent experiments of Anderson, Haymaker and Joseph have shown that the life of adrenalectomized rats may be prolonged beyond the survival period of untreated controls if such rats are injected with benzene extracts of blood taken from patients having hyperadrenalo-cortical syndrome (Cushing's Disease). What I meant to imply is that if this is true for patients with hyperadrenalo-cortical syndrome, it may very well hold for patients who have suprarenal cortical tumors either within the suprarenals or arising in misplaced suprarenal cortical tissues in the ovary. This may form a basis for differentiating suprarenal cortical tumors (hypernephroma) and lutein cell blastomas.

If the tumor in question arises from misplaced suprarenal cortical cells, we should expect to find adrenosterone in the tumor, which is closely related to testosterone. If the tumor in question is a lutein cell blastoma we should expect to find progesterone within the tumor. However, testosterone, adrenosterone, and progesterone are very closely related. Qualitatively there is very little difference between them, though they may be differentiated quantitatively.

DR. SCHILLER (closing).—It is a fact that the ovaries develop substances of virilizing effect and that testicles produce folliculin. What holds for physiologic tissue may be found in even a higher degree in tumors developing from it. For this reason, I think it is not safe to prove the origin of a virilizing or masculinizing tumor by its production of substances of sex influencing capacity. To classify such tumors for the time being, it is much safer to rely on morphologic criteria exclusively.

THE THERAPEUTIC VALUE OF LOW-DOSAGE IRRADIATION OF THE PITUITARY GLAND AND OVARIES IN FUNCTIONAL MENSTRUAL DISORDERS AND STERILITY*

CHARLES MAZER, M.D., AND GEORGE BAER, M.D., PHILADELPHIA, PA.

IN NO other branch of gynecology is roentgen ray irradiation more helpful and promising than in the treatment of functional menstrual disturbances. Depending on the dose employed, it is equally effective in stimulating or suppressing the menstrual function as the indication may be.

As early as 1915, Van de Velde[1] employed roentgen rays for the purpose of stimulating the menstrual function. In 1922, Hofbauer[2] successfully employed irradiation of the pituitary gland in the treatment of dysfunctional uterine bleeding. Since then several investigators have reported with added enthusiasm on the striking effectiveness of roentgen rays in restoring menstrual rhythm (Table I). There, nevertheless, still exists an insurmountable hesitancy on the part of gynecologists to employ this valuable agent because of the misconception that roentgen rays, regardless of dosage, always destroy cellular function.

DeLee and Greenhill[3] summarize these divergent opinions as follows: "The feeling about the use of x-ray treatment to overcome amenorrhea and sterility is somewhat analogous to the sentiment about radiating the pituitary gland to combat menopausal symptoms. Those who favor x-ray treatment are most enthusiastic about it, but a large proportion of those who do not use this treatment, condemn it in no uncertain terms. One thing is true, there is no *apparent* immediate harm from x-ray treatment in most cases, although sometimes permanent amenorrhea occurs. Whether any remote adverse effects will appear from such treatment is theoretical. Of course, only a skilled roentgenologist should be called in to treat women who want to overcome sterility and amenorrhea."

INDICATIONS FOR AND CONTRAINDICATIONS TO LOW-DOSAGE IRRADIATION OF THE PITUITARY GLAND AND OVARIES

Amenorrhea and abnormal uterine bleeding, not caused by organic disease of either constitutional or local origin, in women of childbearing age are amenable to low-dosage irradiation. It is also the most effective measure in the control of intractable bleeding during puberty.

An associated pelvic inflammatory condition is always a contraindication to therapeutic irradiation of the ovaries.

In view of the known deleterious effects of postconception, pelvic irradiation on the offspring (Goldstein and Murphy,[4]), the possible presence of early pregnancy should be definitely excluded before exposing the ovaries to x-rays for the relief of amenorrhea. Moreover, in order to avoid the occurrence of conception and possible injury to the offspring

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during the course of roentgen ray treatment, sexual relations should be forbidden until the final treatment has been given.

Unlike Ford and Nelson[5] and Newell and Pettit,[6] we found that dysmenorrhea per se is only occasionally relieved by low-dosage irradiation of the pituitary gland and ovaries. Hypomenorrhea and pseudomenstruation in women with a normal menstrual rhythm are likewise refractory to this form of treatment. Inasmuch as these conditions are occasionally precursors of amenorrhea, its subsequent occurrence may erroneously be attributed to such irradiation.

MODE OF ACTION OF LOW-DOSAGE IRRADIATION OF ENDOCRINE GLANDS

The term "stimulation therapy" is applied to this type of x-ray treatment because of the apparent increase in hormone production and acceleration of function of the irradiated gland without cytologic changes demonstrable by the instruments at our disposal. Epifanio and Cola,[7] for instance, observed a rapid increase of growth in young rabbits after low-dosage irradiation of the pituitary gland which at autopsy showed no evidence of cytologic alterations.

That doses of roentgen rays within the limits employed in this type of therapy produce no visible cytologic changes in the ovaries, either immediate or remote, was shown in treated rats by Drips[8] and in 38 young women who were irradiated five to seven days before hysterectomy for carcinoma of the cervix by Wagner and Schoenhof.[9] That the secreting elements of endocrine glands may overfunction or underfunction without evident alterations in cell structure is strikingly illustrated by the absence of histologic changes in the islands of Langerhans in some cases of hyperinsulinism and in nearly half of the diabetics who come to autopsy. It is, therefore, apparent that biochemical factors alone, such as cell permeability and rearrangement of electrons, atoms, and molecules, often determine the degree of cellular activity.

Thäler,[10] Desjardins,[11] and others dispute the power of roentgen rays to stimulate the function of living cells. They believe that the beneficial effect of low-dosage irradiation in the treatment of amenorrhea is the result of destruction by the rays of a persistent corpus luteum which, in their opinion, is often the cause of amenorrhea. A persistent corpus luteum is, however, a rarity in the human being and, when present, is followed by menstruation within thirty-six hours after its removal. No such immediate effect occurs in women irradiated for amenorrhea. Restoration of menstrual function by low-dosage irradiation of the pituitary gland alone (Steinhardt,[12] and Werner[13]) certainly cannot be attributed to destruction of an inhibitory factor because there is nothing in the pituitary gland to actively inhibit menstruation, except the rare presence of an adenoma which would not respond to such small doses of x-rays.

Hirsch[14] suggests that the stimulative effect of low-dosage irradiation on the endometrium cannot be entirely excluded as a contributing factor in the production of good results in women with marked uterine hypoplasia.

SAFETY OF LOW-DOSAGE IRRADIATION OF THE OVARIES

Even massive irradiation of the pituitary gland, as employed in the treatment of adenomas, is known to produce no ill effects on the secreting elements of the hypophysis. The profession as a whole and roentgenologists in particular are reluctant, however, to expose the ovaries even to mild irradiation because of the reports of Frank[15] and others that the temporary amenorrhea of some patients had become permanent as a result of such treatment. A temporary adverse effect to low-dosage irradiation of the ovaries occurred in only 7 of 480 patients under our observation. It is possible, moreover, that these partly amenorrheic women would have developed a more permanent amenorrhea without the use of roentgen therapy. It is evident, therefore, that possible harmful effects can be more accurately evaluated in regularly menstruating women subjected to similar ovarian irradiation. We have previously reported that the normal menstrual rhythm of 11 patients was not affected by properly administered, low-dosage irradiation of the ovaries (Mazer and Spitz[16]). In the present series, there is an additional group of 28 regularly menstruating women who were subjected to low-dosage irradiation with temporary interruption of the menstrual rhythm in one. Further evidence of the harmlessness of the procedure is revealed in the fact that none of the patients who had received more than one course of x-ray exposures at intervals of three months became permanently amenorrheic and that most of them were restored to normal menstrual periodicity. It must, nevertheless, be emphasized that the margin between a safe and a harmful dose is probably limited and that variations in dosage should, for the present, not be attempted.

A survey of the available literature, as summarized in Table I, reveals no ill effects on the offspring following preconception irradiation within the limits of dosage employed in this type of therapy. The number of abortions is also relatively small and well within the usual average incidence. In fact, even heavy preconception irradiation of human ovaries was found to have no baneful effects on offspring of the first generation (Goldstein and Murphy,[4] and Nürnberger[17]). The problem of damage to human germ cells by heavy irradiation, however, still lacks the necessary fundamentals for proper solution. Statistical material is still insufficient for positive conclusions regarding mutations following heavy irradiation. The foregoing remarks concerning heavy irradiation are, however, not applicable to the small doses employed in the treatment of menstrual disorders.

TECHNIQUE OF LOW-DOSAGE IRRADIATION OF THE PITUITARY GLAND AND OVARIES

When ovarian hypofunction is secondary to a pituitary deficiency, such as Froehlich's syndrome, x-ray exposure of the hypophysis alone yields fairly good results (Steinhardt,[12] Werner,[13] and Mazer and Spitz[16]). Simultaneous irradiation of the ovaries does, however, increase the percentage of cures by rendering the ovaries more responsive to the enhanced pituitary stimulation (Table I). In instances of primary ovarian deficiency, irradiation of the ovaries alone is sufficient treatment. The

incidence in amenorrhea of a primary ovarian defect, totally independent of the pituitary gland, is, however, relatively small (about 20 per cent).

TABLE I. STATISTICS ON ROENTGEN RAY TREATMENT OF AMENORRHEA

Note: Improved cases grouped as failures

REPORTED BY	DURATION OF AMENORRHEA	AGE OF PATIENTS	GLAND IRRADIATED	NO. OF PATIENTS	NO. OF CURES FOR 1 OR MORE YEARS	NO. OF HEALTHY OFFSPRING	NO. OF ABORTIONS
Thäler[10]	4 to 30 mo.	17 to 35 yr.	Ovary	62	40 (65%)	2	-
Werner[13]	-	-	Pituitary	13	7 (54%)	-	-
Steinhardt[12]	3 to 54 mo.	18 to 39 yr.	Pituitary	50	22 (44%)	2	-
Kaplan[19]	1 mo. to 14 yr.	19 to 45 yr.	Pituitary and ovaries	117	79 (67%)	38	5
Drips[21]	-	29 single and 33 married women	Pituitary and ovaries	62	31 (50%)	11	-
Tamis[25]	3 to 36 mo.	17 to 36 yr.	Pituitary and ovaries	25	15 (60%)	-	-
Edeiken[26]	-	-	Pituitary and ovaries	56	40 (72%)	11	1
Rubin[27]	-	19 to 33 yr.	Pituitary and ovaries	12	11 (93%)	8	1
Rongy[28]	2 to 3 mo.	-	Pituitary and ovaries	13	5 (37%)	-	-
Porchownik[20]	-	16 to 39 yr.	Pituitary and ovaries	73	23 (31%)	20	6
Mazer and Goldstein (1932)	3 to 36 mo.	20 to 35 yr.	Pituitary and ovaries	58	38 (66%)	20	5
Mazer and Spitz (1935)	1 to 6 yr.	18 to 36 yr.	Pituitary and ovaries	74	41 (55%)	26	2
Mazer and Baer (1938)	1 to 13 yr.	18 to 36 yr.	Pituitary and ovaries	106	62 (59%)	20	4

The differential diagnosis between a primary pituitary and a primary ovarian amenorrhea is, moreover, difficult, requiring not only experience but the use of extensive laboratory procedures. It is therefore clinically expedient to irradiate the pituitary gland and ovaries in all amenorrheic patients showing no constitutional or pelvic condition.

The x-ray dosage employed by the various investigators is almost uniform. The technique employed in the present series, as well as in the two previously reported (Mazer and Goldstein,[18] and Mazer and Spitz[16]), is as follows: 135 kv., 5 ma. at a distance of 40 cm. with 6 mm. of aluminum filtration through a field of 20 by 20 cm. The rays are directed over the anterior pelvic area. Depending upon

the thickness of the pelvis, 60 to 90 r. units measured in air are given to the skin. This is repeated at intervals of one week, three times. The total dose reaching the ovaries is about 10 per cent of a full skin erythema. The pituitary gland is treated with the same dosage and factors through a field 3 by 3 cm. simultaneously.

Kaplan[19] uses high voltage rays, the factors being 200 kv., 5 ma. with 0.5 mm. Cu plus 1 mm. Al filter at 30, 40 or 50 cm. distance and through fields of 8 by 10, 9 by 12, 10 by 15 cm. The rays are directed through the right and left anterior and posterior pelvic areas over the ovaries. Seventy-five to 100 r. per area per treatment being given to each area once a week. Alternately anterior and posterior areas are treated at weekly intervals for three treatments. In addition he gives one or two treatments of 75 to 100 r. to the forehead over the pituitary area. This is also administered simultaneously with a pelvic treatment.

ANALYSIS OF INDICATIONS AND RESULTS IN 178 PATIENTS TREATED BY MEANS OF LOW-DOSAGE IRRADIATION OF THE PITUITARY GLAND AND OVARIES

The present series comprises a group of 178 women who were treated by means of low-dosage irradiation during the years 1935 to 1937, inclusive. The technique did not differ from that employed in the previously reported 2 groups of patients (Mazer and Goldstein,[18] and Mazer and Spitz[16]). Of the 178 women, 106 had amenorrhea of varying severity, 3 had normal menstrual rhythm but a scanty flow, 26 had menorrhagia and 18 metrorrhagia. The remaining 25 patients had normal menstrual rhythm but were irradiated for abnormalities such as sterility, dysmenorrhea, premenstrual tension, and migraine.

SELECTION OF THE CLINICAL MATERIAL

Patients were carefully examined to exclude etiologic factors unrelated to pituitary and ovarian deficiencies. The possible presence of an early pregnancy was eliminated by physical examination and the Friedman pregnancy test. Cured patients who received simultaneously with x-ray treatment some form of organotherapy are excluded from this study on the assumption that the latter may have contributed to the good results. On the other hand, patients who failed to respond to combined roentgen ray and endocrine therapy are included in the list of failures because of our conviction that the endocrine products were not responsible for the lack of response to irradiation. Those who failed to respond within two months after irradiation or who conceived soon after treatment are also excluded from the list of cures on the assumption that the results were incidental and not attributable to the irradiation. All patients were followed for a period of one or more years. Instances of improvement or restoration of the menstrual function for a period less than a year are grouped as failures. Adherence to these rigid requirements, set up as a guard against erroneous deductions, justifies the presentation of this report.

EFFECT ON PRIMARY AMENORRHEA

Five patients, ranging in age from 17 to 24 years, had never menstruated. None of them showed the cyclic presence of estrogen in either the blood or urine. The one who responded favorably was 18 years old and typically hypogonad (underweight, visceroptotic, and relatively long-limbed). Her first period appeared three

days after the last of 3 irradiations of the pituitary glands and ovaries. She has been menstruating regularly during a follow-up period of twenty-three months. A co-existing Müllerian defect (endometrial atrophy) which is probably present in all instances of primary amenorrhea was demonstrated in 1 of the 4 patients who failed to respond to treatment. She received nearly a half million rat units of estrogen over a period of two months, despite which curettage failed to recover sufficient endometrium for examination. The nonresponsiveness of patients with primary amenorrhea to low-dosage irradiation was also noted by Porchownik.[20]

EFFECT ON SEVERE SECONDARY AMENORRHEA

Sixty-one treated patients, ranging in age from 18 to 36 years, were followed for periods of from one to three years. Thirty-three (54 per cent) were restored to normal menstrual periodicity, 5 were improved and 4 conceived too soon after treatment to permit an evaluation of the treatment. The remaining 19 failed to respond but were not made worse by the treatment. The duration of the amenorrhea in this group of 61 patients ranged from six months to thirteen years (average 3.9 years).

The response to low-dosage irradiation seems to be inversely proportional to the duration of the disorder. Only 2 of the 10 women (20 per cent) who had no menstrual flow for a period of two years and only 5 of 11 (45 per cent) who had no menstruation for a year prior to treatment were restored to normal menstrual periodicity. Whereas, 26 of the remaining 40 patients (63 per cent) who had one or two menstrual periods during the year immediately preceding treatment were cured.

Other factors influencing the results of low-dosage irradiation are the degree of uterine hypoplasia and the cyclic presence or absence of estrogen in the blood and urine. This is shown by the fact that the 19 complete failures were among the 29 patients who showed a high degree of genital hypoplasia and an absence of a demonstrable quantity of estrogen in the blood and urine. The uteri of such patients require intensive priming with estrogen before or after irradiation.

Twenty-nine of the 61 patients in this group were sterile. Fourteen of them conceived within one year following irradiation. Ten of the 14 delivered healthy offspring, 3 aborted and 1 is still pregnant.

EFFECT ON OLIGOMENORRHEA

The normal length of the human menstrual cycle varies ordinarily from twenty-one to forty days. Menstrual intervals of from seven to thirteen weeks, representing a moderate delay in menstruation, are justifiably considered ab-

TABLE II. RESULTS OF LOW-DOSAGE IRRADIATION IN 153 WOMEN WITH DYSFUNCTIONAL MENSTRUAL DISORDERS*

MENSTRUAL DISORDER	NO. OF PATIENTS	AVERAGE AGE OF PATIENTS (YR.)	AVERAGE DURATION OF MENSTRUAL DISORDER IN YEARS	RESULTS	
				CURED	FAILURE
Primary amenorrhea	5	19.2	Since puberty	1 (20%)	4
Severe secondary amenorrhea	61	25.2	3.9	33 (54%)	28
Oligomenorrhea	40	25.8	7.4	28 (70%)	12
Hypomenorrhea	3	26.0	10.8	0	3
Menorrhagia	26	24.6	2.9	15 (57%)	11
Metrorrhagia	18	27.6	1.2	16 (89%)	2
Totals	153			93	60

*NOTE: Patients followed for one or more years. Improvement or incidental pregnancy listed as failure.

normal. This irregularity, termed oligomenorrhea, connotes a milder form of ovarian deficiency than that of frank amenorrhea and yields more readily to treatment. Forty patients with oligomenorrhea, ranging in age from 18 to 38

years, were treated by means of low-dosage irradiation. Twenty-eight of the 40 patients (70 per cent) have since been menstruating at normal intervals during a follow-up period of from one to three years, 3 conceived too soon after treatment to permit proper evaluation, 7 were unaffected by the irradiation, and the remaining 2 were apparently adversely affected inasmuch as their menstrual intervals have been longer since the treatment.

The fact that only 13 of the 40 patients with oligomenorrhea had evident genital hypoplasia and no demonstrable estrogen in either the blood or urine apparently accounts for the high percentage of cures in this group. Twenty-one of the group of 40 patients were involuntarily sterile and of these, 9 conceived within one year of treatment and bore healthy offspring. The pregnancy of another ended in abortion.

It is interesting to note the relative responsiveness of the 3 types of amenorrhea to low-dosage irradiation. The treatment yielded only 20 per cent of a lasting cure in primary amenorrhea, 54 per cent in secondary amenorrhea, and fully 70 per cent in the milder form of amenorrhea, known as oligomenorrhea. Of the 106 patients in the 3 groups, 62 or 59 per cent were restored to a normal menstrual rhythm during a follow-up period of from one to three years. It is, moreover, possible that the 7 of the 44 classified as failures may have benefited considerably from the treatment, since they conceived within one or two months without the aid of any other agent.

Illustrative of the importance of not relying solely on a pelvic examination to determine the presence or absence of early pregnancy before resorting to low-dosage irradiation of the ovaries, are 4 patients not included in this study because they came under our observation after they had already received postconceptional irradiation for mistaken amenorrhea. Only 1 of the 4 was delivered of a live and healthy infant. Of the remaining 3 women, 1 was delivered of a monster, 1 of a stillborn caused by an antenatal pneumonia, and the last one, of a premature stillborn because of polyhydramnios.

EFFECT ON METRORRHAGIA

The choice of measures usually employed in successfully combating dysfunctional uterine bleeding not only depends upon a knowledge of the gland primarily responsible for the disorder but also on the age of the patient. Abnormal uterine bleeding at or near the menopause, an age when malignancy is often encountered, is best treated by means of an exploratory curettage and the intrauterine application of from 600 to 1200 mg. hours of radium. This dual procedure is both diagnostic and curative. If the endometrium shows evidence of malignancy, subsequent hysterectomy is the logical measure to employ.

Dysfunctional uterine bleeding during the puberal and childbearing years is usually treated by means of small doses of desiccated thyroid and hypodermic administration of the anterior pituitary-like substance obtained from the urine of pregnant women. The use of even small doses of radium, such as 150 or 200 mg. hours (Drips,[21] Keene and Payne,[22] and Schulze[23]) is, to say the least, a radical measure. Radium, even in such small doses, produces temporary amenorrhea for periods varying from three to twelve months in more than 20 per cent of the patients (Keene and Payne,[22] and Schulze[23]) and exerts a baneful effect on fertility. The intrauterine application of radium causes fibrosis of the intima in the uterine blood vessels—a condition incompatible with subsequent normal function of the endometrium. This sclerosing effect of radium is not only evident microscopically but also in the functional response of such an irradiated endometrium to large doses of estrogen. For instance, following intrauterine application of radium in menopausal women, no amount of estrogen causes uterine bleeding. On the other hand, after surgical castration, even fractional doses of estrogen result in uterine bleeding.

Few investigators have thus far employed low-dosage irradiation in the treatment of dysfunctional uterine bleeding of puberal girls and of women of childbearing age. Drips[21] employed it in only 4 patients with improvement in 3. Molinari and Vierheller[24] obtained a cure of dysfunctional bleeding in 21 of 46

patients by irradiation of either the pituitary gland, ovaries, or of both. Thäler[10] cured 11 of 32 patients by means of low-dosage irradiation of the ovaries only. Lifewise, in our experience, this is an effective and harmless measure in intractable dysfunctional uterine bleeding of adolescent girls and women of childbearing age.

Eighteen patients, ranging in age from 14 to 34, were subjected to low-dosage irradiation of the pituitary gland and ovaries for relief of metrorrhagia after all other measures had failed. In 6, menstrual rhythm was normal prior to the onset of the metrorrhagia; in the remaining 12, it was irregular (usually delayed about two or three months). Of the 6 who prior to the onset of metrorrhagia were menstruating regularly, 5 were cured and 1 was not benefited by the treatment. Of the 12 whose menstrual rhythm was abnormal prior to the onset of metrorrhagia, all but 1 were relieved of the metrorrhagia but only 8 were restored to menstrual periodicity by the treatment. One of these 18 patients conceived within a year of the irradiation and bore a healthy infant. The 2 failures (11 per cent) were in the group of 4 puberal girls who had bled severely for months.

Only 5 of the 18 women with metrorrhagia were curetted prior to the administration of low-dosage irradiation. The history of one of the 5 is unusually interesting and deserves recording:

S. B., aged 32, the wife of a physician and the mother of a 9-year-old child, menstruated normally until July, 1936. Thereafter she bled almost continuously until she was irradiated in January, 1937. During the period of abnormal bleeding, she was curetted 3 times and also received organotherapy without relief. Since the irradiation (two years), she has been menstruating normally.

EFFECT ON MENORRHAGIA

It is universally accepted that the normal duration of the menstrual flow should not exceed eight days. The tendency to prolonged and excessive bleeding without apparent cause is especially marked in puberal and adolescent girls. Twenty-six patients, ranging in age from 14 to 25 years, had menorrhagia without apparent cause for an average duration of thirty-two months. Organotherapy in all of them and curettage in 14 had failed to arrest the excessive bleeding. A study of the endometrium obtained by curettage premenstrually in 14 of the 26 patients throws considerable light on the etiology of the condition. There was no evidence of the secretory phase in any of them. In 10, the endometrium was hyperplastic and, in the remaining 4, it was of the interval type.

Fifteen of the 26 patients (57 per cent), among whom were 2 of puberal age, were relieved of the menorrhagia by low-dosage irradiation during a follow-up period of eighteen months. Four were improved, 6 were unaffected, and the remaining 1 conceived too soon after x-ray treatment to permit evaluation of its effectiveness. It is noteworthy that none of the 26 patients became amenorrheic following the roentgen treatment.

EFFECT ON HYPOMENORRHEA

Hypomenorrhea (cyclic bleeding with scanty flow) is usually undisturbing to the patient until offspring is desired. Our hesitancy to subject patients with this form of menstrual disturbance to irradiation has been noted in the foregoing paragraphs. Only 3 sterile women with hypomenorrhea were irradiated. One conceived soon after treatment and carried successfully to term. The other 2 were unaffected by the treatment.

EFFECT ON REGULARLY MENSTRUATING WOMEN

Twenty-six patients with normal menstrual cycles were irradiated for conditions not directly related to the menstrual rhythm. Seventeen were irradiated in the hope of relieving sterility without an accountable cause, with success in only 4. Four of the 26 women were treated for dysmenorrhea with relief in 2. Three others were irradiated in the hope of alleviating the ill-defined syndrome known as "premenstrual tension"; 2 of them were relieved. The remaining 2 patients of this group of 26 had severe premenstrual migraine; 1 was totally relieved.

Low-dosage irradiation of the pituitary gland and ovaries in this group of 26 regularly menstruating women resulted in a temporary, though definite, delay in the menstrual flow of one who, however, had in the past shown a tendency to amenorrhea. Nevertheless, it again points to the probability that the margin of safety in ovarian irradiation is small and that larger doses should not be employed for the present.

SUMMARY

Low-dosage irradiation of the pituitary gland and ovaries resulted in restoration of the menstrual function in 59 per cent of 106 cases of amenorrhea, 89 per cent of 18 cases of dysfunctional metrorrhagia during the childbearing age and in 57 per cent of 26 cases of dysfunctional menorrhagia. It had no effect in 3 cases of hypomenorrhea. The amenorrhea of 2 patients was presumably aggravated by the treatment.

Low-dosage irradiation of the pituitary gland and ovaries in 26 women with normal menstrual cycles resulted in temporary amenorrhea of one who, however, had in the past shown a tendency to amenorrhea.

Low-dosage irradiation of the pituitary gland and ovaries is highly effective in sterility of women with functional menstrual disorders but has very little, if any, effect in those who menstruate normally.

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2047 Spruce Street

DISCUSSION

DR. FRANKLIN L. PAYNE.—In the cases of amenorrhea upon which Dr. Mazer has done estrin determinations, the ones showing adequate quantities of estrin were more likely to respond to irradiation than those with hypoestrinism. This may be the crux of the treatment of amenorrhea by irradiation.

Functional amenorrhea is a symptom which may result from any one of many combinations of endocrine dysfunction. Study of a large number of amenorrheic patients at the University of Pennsylvania Hospital demonstrated that 47 per cent had normal or excessive quantities of estrin in the blood and the urine. Endometrial biopsies in a considerable number of these showed proliferative changes and a few showed hyperplasia. It is likely that amenorrheic patients with adequate or

excessive quantities of estrin and proliferative or hyperplastic endometrium will respond to roentgen therapy. It is unlikely that those with hypoestrinism will be benefited and they may be harmed.

DR. CHARLES MAZER.—At a very low cost to the patient, the roentgenologist conversant with the technique of this type of treatment will return to you 54 per cent or more of your patients with permanently restored menstrual function. As compared with organotherapy which yields no more than 10 or 15 per cent of cures, low-dosage irradiation of the pituitary gland and ovaries is the procedure of choice in the treatment of functional menstrual disorders.

Blood and urine studies for estrogen are unreliable because we must of necessity employ too few rats for each titration. The degree of uterine atrophy accurately reflects the level of estrogen production and guides the clinician as to the need of estrogen for the purpose of stimulating the Müllerian tract.

THE EFFECT OF THE FEMALE HORMONES AND OF PREGNANCY UPON THE URETERS OF LOWER ANIMALS AS DEMONSTRATED BY INTRAVENOUS UROGRAPHY*

FRANKLIN L. PAYNE, M.D., AND PHILIP J. HODES, M.D.,
PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and Department of Radiology, Hospital of the University of Pennsylvania)

THE purpose of this communication is to report the results of a series of experiments which were conducted in the effort to produce ureteral dilatation in rabbits and dogs, by means of injections of pregnancy prolan, estrin and progesterone and to report the effect of pregnancy upon the ureters of these animals.

The occurrence of varying degrees of ureteral dilatation in human beings during pregnancy has been recognized for years. The exact mechanism which is involved in the production of these changes has remained unidentified. Among the explanations which have been offered may be listed such anatomic variations incident to pregnancy as uterine pressure, pelvic congestion, bladder distortion and uterine dextrorotation.[1] Primary terminal ureteral hypertrophy also has been suspected of contributing to these alterations.[2] These explanations have been partially discredited by recent investigations[3-5] which demonstrated that the abdominal ureters are flaccid and distended rather than hypertrophied during pregnancy. The similarity between this atony and the uterine relaxation of pregnancy has led some men[3-5] to suspect a common etiologic factor, possibly hormonal in nature. This theory has not been substantiated experimentally, however. Spayed dogs have been injected with estrin without producing significant ureteral changes.[4]

METHOD

With a satisfactory technique for intravenous urography in lower animals, it was decided to pursue these investigations further by using the more highly concentrated hormones which are now available. Control urograms were made before each series of injections. At the completion of each experiment, the ureters were examined grossly and microscopically for evidence of dilatation.

Diodrast was used routinely as the contrast medium. The dosage was not accurately standardized by body weight for each animal: 5 c.c. were used in rabbits

*Read at a meeting of the Obstetrical Society of Philadelphia, December 1, 1938.

and 10 c.c. in dogs. Injections were made into a leg vein in the dogs and into an ear vein in the rabbits, with no attempt to prolong the period of introduction. In spite of this, no untoward reactions were noticed. At completion of the injections, the animals were fixed upon a board in the supine posture and immediately placed in an extreme Trendelenburg position with the plane of the board sixty degrees to the horizontal. The physical factors employed were as follows: 100 ma.; 60 to 70 kv; 1/15 to 1/20 second; 30-inch target film distance. A fine focus rotating anode tube and casettes with double intensifying screens were used.

During the early period of these studies, each animal was radiographed at four-, seven-, ten-, and fifteen-minute intervals. More recently, only the seven- and ten-minute examinations were made, as it was found that the four- and fifteen-minute exposures added nothing to the urographic study.

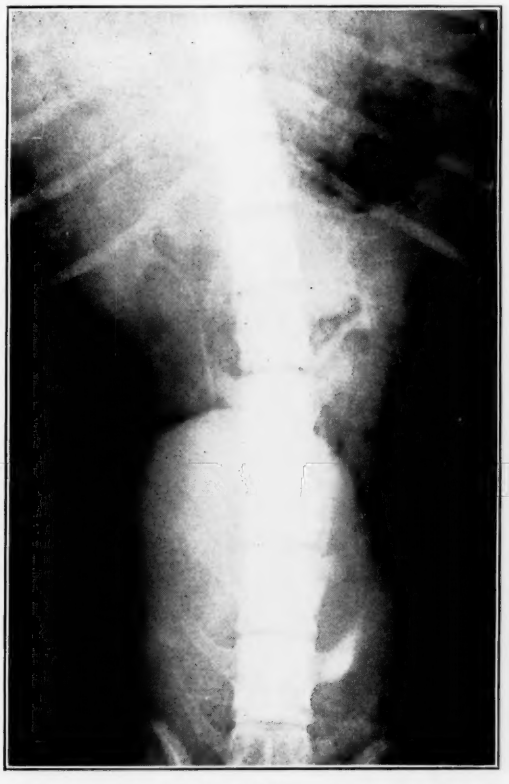

Fig. 1.—Urogram of dog after 44,000 B.D.U. of pregnancy prolan. No ureteral dilatation.

The excellent visualization of the upper urinary tract which resulted from this method made it unnecessary to resort to abdominal compression or purgation[7] in order to obtain satisfactory renal and ureteral detail.

The results obtained on dogs and rabbits following injections of pregnancy prolan are tabulated in Table I. Urograms, which were made at intervals of seven to ten days (Fig. 1), revealed no evidence of ureteral dilatation. Sections through the upper, middle, and lower portions of the ureters revealed no significant deviation from the normal.

Injections of estrin also failed to produce ureteral dilatation (Table II). Urograms were obtained at intervals of fifteen days during the experiment and subsequent microscopic study of the ureters confirmed the x-ray findings.

Twenty international units of progesterone were injected into each of two rabbits over a period of twenty days. The results, which are tabulated in Table III, were

negative. The absence of ureteral dilatation, as demonstrated roentgenographically in Fig. 2, was verified by post-mortem gross and microscopic examination.

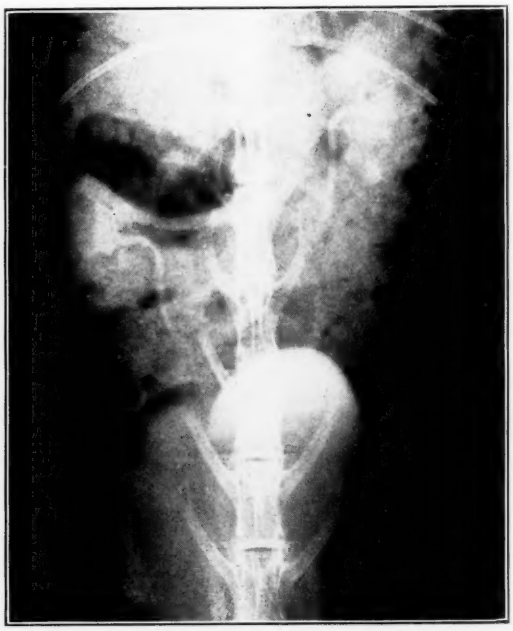

Fig. 2.—Urogram of rabbit which had received 20 I.U. of progesterone. No ureteral dilatation.

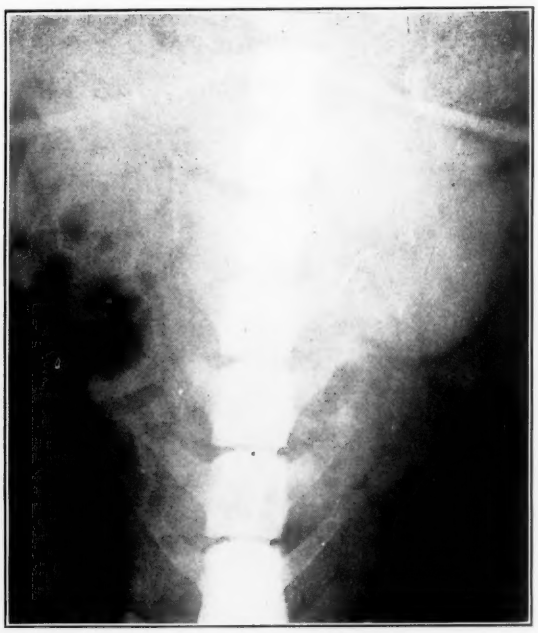

Fig. 3.—Urogram of a dog in the seventh week of gestation. No ureteral dilatation.

TABLE I. EFFECT OF PREGNANCY PROLAN

ANIMAL	NO. OF INJECTIONS	TOTAL DOSAGE	TOTAL TIME	UROGRAMS	
				NUMBER	RESULTS
Dog 25	22	44,000 B.D.U.*	44 Days	5	No dilatation
Dog 528	22	44,000 B.D.U.	44 Days	5	No dilatation
Rab. 4	6	1,350 B.D.U.	14 Days	2	No dilatation
Rab. 5	6	1,350 B.D.U.	14 Days	2	No dilatation
Rab. 6	9	9,000 B.D.U.	20 Days	2	No dilatation
Rab. 7	9	9,000 B.D.U.	20 Days	2	No dilatation

*B. D. U., Biologic day units.

TABLE II. EFFECT OF ESTRIN

ANIMAL	NO. OF INJECTIONS	TOTAL DOSAGE	TOTAL TIME	UROGRAMS	
				NUMBER	RESULTS
Dog 25	9	18,000 R.U.	47 Days	3	No dilatation
Dog 528	9	18,000 R.U.	47 Days	3	No dilatation

TABLE III. EFFECT OF PROGESTERONE

ANIMAL	NO. OF INJECTIONS	TOTAL DOSAGE	TOTAL TIME	UROGRAMS	
				NUMBER	RESULTS
Rab. 10	4	20 I.U.	20 Days	2	No dilatation
Rab. 11	4	20 I.U.	20 Days	2	No dilatation

The effect of pregnancy has been studied previously by Mengert,[6] who reported that examination of post-mortem specimens disclosed no appreciable differences between the ureters of pregnant and nonpregnant lower animals. Our urographic studies in six pregnant animals, which are summarized in Table IV, support Mengert's findings. Since the average period of gestation is sixty days in dogs and thirty days in rabbits, it is obvious that the pregnancies were well advanced at the time of the urographic examinations. Fig. 3, showing no ureteral dilatation, is that of a dog in the sixth week of gestation.

COMMENT

The number of experiments included in each group is too small to be of statistical importance. The uniformly negative results, however, seem to indicate that the hormones which were injected are not capable of producing ureteral changes in dogs and rabbits. It is possible that insufficient quantities of these agents were used or that sufficient time did not elapse between the first injection and the last urogram. Since ureteral dilatation does not occur during pregnancy in dogs or rabbits, it is unlikely that this change can be produced in these animals by any type, or combination, of hormone medication.

TABLE IV. EFFECT OF NORMAL PREGNANCY

ANIMAL	LENGTH OF PREGNANCY	UROGRAM
Dog 384	6 Weeks	No dilatation
Dog 368	7 Weeks	No dilatation
Dog 519	6 Weeks	No dilatation
Dog 695	Well advanced	No dilatation
Rab. 8	3 Weeks	No dilatation
Rab. 9	3 Weeks	No dilatation

SUMMARY

1. A method for obtaining intravenous urograms in lower animals is described.

2. Attempts to produce ureteral dilatation in rabbits and dogs by hormone injections have been unsuccessful.

3. Urographic examinations of pregnant dogs and rabbits have revealed no evidence of ureteral dilatation.

We wish to express our gratitude to Drs. F. E. Keene and E. P. Pendergrass for their continued interest during this study. We are also indebted to the following contributors: Research Department, Winthrop Chemical Company for a generous supply of diodrast; Ayerst, McKenna and Harrison for an ample quantity of anterior pituitary-like hormone; Schering Corporation for an adequate amount of progynon B.

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THE POSTMATURE FETUS*

John Casagrande, M.D., Brooklyn, N. Y.

(From the Department of Obstetrics and Gynecology of the Brooklyn Hospital)

THE postmature fetus may be defined as an overdeveloped fetus near or beyond term or any fetus born well beyond the expected date of labor.

I have gone over the histories of all large babies weighing 9 pounds (4072 gm.) or more delivered at The Brooklyn Hospital from 1935 to 1937 inclusive, in an effort to determine the risk involved to the mother and fetus.

Table I. Deliveries 1935 to 1937 Inclusive

			FETAL MORTALITY (UNCORRECTED)	FETAL MORTALITY (CORRECTED)
Total deliveries	3314	160	4.83%	2.03%
Group I (9 to 10 pounds)	157	6	3.82%	3.18%
Group II (10 pounds and over)	30	4	13.33%	13.33%

During this period, 3,314 babies were delivered. There were 160 stillbirths and neonatal deaths. The corrected fetal mortality was 2.03 per cent.

Those weighing 9 pounds (4072 gm.) or more were classified as postmature from the standpoint of development. Of these, there were 187 which were divided into two classes.

Group I weighed between 9 and 10 pounds, of which there were 157, and 6 babies were lost. The corrected fetal mortality was 3.18 per cent which is about 50 per cent higher than for the entire series. No further analysis was made of this group

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other than noting that three sections were done which practically corresponds to the average number of sections done for the whole three-year series.

Group II included all babies weighing 10 pounds (4,800 gm.) or more, the analysis of which is given in greater detail. Thirty babies were delivered in this series with a fetal mortality of 4, or 13.33 per cent. This much higher mortality was found to be due mainly to the difficulty encountered in the delivery of the shoulders. There were 18 multiparas with an average labor of eight hours and twenty-seven minutes. The 12 primiparas had an average labor of twenty-three hours and twelve minutes. The presentations were vertex, of which 13 were posterior, two were transverse and 15 were anterior. The pelvic measurements were classified as ample in 26 and no classification given in 4.

TABLE II. GROUP II. BABIES WEIGHING 10 POUNDS OR MORE

	PREMATURE	POSTMATURE	EXPECTED DATE NOT RECORDED
Less than 1 week	5	5	3
1-2 weeks	2	6	
2-3 weeks	2	5	
3-4 weeks	1	0	
5-6 weeks	0	1	

From the menstrual history 17 were overdue; one patient went thirty-six days beyond her expected time and her baby weighed 10 pounds 14½ ounces. Accurate data were not obtained in three patients. Ten delivered before the expected date; one of these delivered twenty-three days early, and the baby weighed 10 pounds 3½ ounces. Labor was induced by castor oil and quinine in 4. The others had a spontaneous onset. Practically all patients received morphine and scopolamine for seminarcosis. In addition some received ether, oil and quinine per rectum.

TABLE III. GROUP II. MODE OF DELIVERY

Cesarean section	2
Midforceps preceded by manual rotation	2
Midforceps	1
Low forceps	3
Perineal forceps	7
Spontaneous	15

Two cesarean sections were done on 2 primiparas following a test of labor. Two babies presenting in the posterior position were converted into anterior position by manual rotation of 180 degrees during the first stage and midforceps extraction was required at a later time in both. Four other cases required extraction, three low forceps and one midforceps. Seven were delivered by forceps control and 15 babies were born spontaneously. Episiotomies were done on 14; first-degree lacerations occurred in 4; second-degree lacerations in 6; 4 had no lacerations. There were 3 female infants and 27 male infants. The relatively large number of male babies in this small series may be a coincidence but the preponderance of male babies in the postmature class has been noted by others. Twenty-five of these patients were service cases and 5 were private. The service deliveries in our hospital usually run a little more than half of the total deliveries. Overeating and lack of exercise have been thought by some to be the cause of overdevelopment of the fetus. It is possible that proper diet and exercise were stressed and more faithfully carried out by the more intelligent private patients, with fewer postmature babies resulting. There were 2 post-partum complications: hemorrhage and a mild phlebitis. During convalescence no patient developed a reportable fever. Twenty-six babies were discharged in good condition. The following is a short summary of 3 stillbirths and a neonatal death:

A 30-year-old, para iii, with an ample pelvis had had two previous labors, both babies weighing over 8 pounds. This baby was born Feb. 5, 1935, and she was

theoretically due Feb. 8. Labor started spontaneously and lasted five hours and twenty-six minutes. The vertex was delivered by manual control and the shoulders were delivered with difficulty by the Kristeller method. The fetal heart was present shortly before delivery. The baby weighed 10 pounds 2½ ounces. An autopsy revealed no apparent cause of death.

A 32-year-old, para i, with an ample pelvis had a spontaneous onset of labor and was delivered ten days after her expected date. After twenty-one hours of labor, the vertex was easily delivered by low forceps. Difficulty was encountered in the delivery of the shoulders, rotation of which was unsuccessful. They were finally delivered by pressure on the fundus. The fetal heart was present before delivery. Death was thought to be due to asphyxia caused by delay in shoulder delivery.

A 34-year-old, para iii, with an ample pelvis had two previous children weighing 9 pounds 7 ounces and 11 pounds 12 ounces, born alive and well. Labor started spontaneously in the L.O.A. position, and the vertex was delivered by manual control twenty-six hours and forty-two minutes after the onset. The shoulders were delivered with difficulty after giving 1 c.c. of pituitrin and using considerable pressure on the fundus. An autopsy showed no apparent cause of death of fetus which weighed 10 pounds 8 ounces.

A 37-year-old, para iii, had two previous babies weighing 11 pounds and 9 pounds were alive and well. Labor was induced by castor oil and quinine, the position being R.O.P. The first stage of labor lasted only three hours, but the pains were very severe; the duration of the second stage, one hour. The delivery was spontaneous. The baby weighed 10 pounds 8 ounces and lived two hours. An autopsy showed laceration of the tentorium cerebelli with hemorrhage.

The etiology of the postmature fetus has been attributed to various factors, such as a familial tendency involving either the mother or father or both. Diet and lack of exercise are considered factors by some. It is commonly stated that multiparas and elderly primiparas are more likely to have large babies. In view of our present knowledge, the postmature fetus resulting from prolonged pregnancy may be due to a hormonal imbalance.

Koff and Davis[1] studied the mechanism of the prolongation of pregnancy in the rabbit and concluded that the corpus luteum hormone or progestin is directly responsible for the maintenance of pregnancy in the rabbit and its normal termination. By injecting pregnancy urine extract to form new corpora lutea or by repeated injections of progestin, they were able to prolong the duration of pregnancy in the rabbit well beyond the customary thirty-two days. When pregnancy was thus prolonged, large postmature fetuses were produced, and, if delivered before the thirty-sixth day, they were alive and normal; if, however, delivered after this date, many of them were dead. Those that survived were large, obviously postmature; the labor was unduly prolonged, sometimes lasting forty-eight to seventy-two hours. They state that this may be due to the excessive size of the offspring but the effect of progestin in diminishing the irritability of the contractile powers of the uterine muscles also may be a factor.

If we are willing to accept that the delivery of a postmature fetus carries a relatively high fetal mortality and possibly a high maternal morbidity, the importance of diagnosing this condition before it has advanced too far is evident. As a guide, we should obtain an accurate history of the last menstrual date. If the patient gives a history of irregular time of menses, especially with periods of amenorrhea, not too much importance can then be attached to the date of the last menstruation. The date of quickening may be of value. Knowledge that the husband is large and a history of previous large babies, should be

noted. Before the diagnosis of a large baby is made, the following should be excluded: twin pregnancy, hydramnios, and pregnancy complicated by tumors. If doubt exists regarding the relative size of the baby after careful abdominal and bimanual palpation, the following measures have been advocated as valuable aids: roentgenograms, cephalometry and mensuration in utero.

The treatment should vary with the individual case. If there is an obvious disproportion, a cesarean section should be done. If it is felt that delivery is possible through the natural passages, induction of labor is advocated by the authors[2-5] whom I have reviewed.

Various methods for induction have been advocated, such as the following: castor oil, quinine, pituitrin, either subcutaneously or intranasally, rupture of the membranes, stripping of the membranes, insertion of a bougie or a bag. Frequently, a combination of these methods is used.

When doubt exists about delivery through the natural passages, radical measures for induction should be avoided so that a section can be done with less risk to the mother should the necessity arrive.

During labor, the patient should receive proper supportive measures. If we are dealing with slow progress in an occipitoposterior position, a rotation of 180 degrees to convert it into an anterior position on the opposite side, in the same oblique diagonal, often hastens the progress of labor with less fetal trauma and simplifies the application of forceps, should it become necessary. Delivery of the shoulders of very large babies is frequently a problem as shown by our mortality. Spontaneous delivery of the vertex is desirable under gas-oxygen analgesia, as this will not interfere with the proper bearing-down pains that are so necessary to deliver the shoulders. Should the pains be insufficient after the head is born, three or four minims of pituitrin may be tried. When forceps has been used to deliver the head and the patient is under a general anesthetic, proper and forceful pressure on the fundus will often deliver the shoulders. Traction on the baby's head should be avoided, as this may readily cause damage to the brachial nerve plexus or spinal cord. Titus describes the following valuable method of the delivery of the shoulders. Between pains insert two or three fingers into the vagina behind the lower shoulder and rotate the axis of the shoulders into the nearest oblique diameter of the pelvis. As the next uterine contraction occurs, traction is made by the fingers in the posterior axilla, pressure is made above the symphysis pubis by the external hand to engage the anterior shoulder, while the nurse or assistant presses firmly downward over the contracted fundus. The pressure should not be made between pains as it is ineffective when not reinforcing a uterine contraction. Moreover, this might cause placental separation. If this fails, the remainder of the examining hand is inserted into the vagina, is passed forward over the shoulder and chest and the posterior arm thus delivered. It is usually flexed at the elbow, and as the hand often comes into view early, it may be grasped, drawn upward and out and the arm delivered by its extention through traction on the arm.

COMMENT

The high fetal mortality in this small series was due mainly to difficulty encountered in the delivery of the shoulders.

When the delivery of a large baby is suspected competent assistance should be present in order to manage properly the delivery of the shoulders.

None of these babies died directly as a result of prolongation of pregnancy as they were all alive just prior to delivery.

The average duration of labor was prolonged.

Maternal morbidity was not high and no serious maternal complications occurred.

Induction of labor may occasionally be justified for prolonged pregnancy resulting in an overdeveloped fetus but each case should be carefully individualized before it is attempted.

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30 Pierrepont St.

DIABETES IN PREGNANCY WITH OBSERVATIONS IN 28 CASES*

Martin M. Shir, M.D., Brooklyn, N. Y.

INSULIN has made pregnancy relatively safe for the diabetic mother. On the other hand, it has complicated the problem because we now see patients with severe diabetes, who in the pre-insulin era would never have been pregnant. Furthermore, insulin has led the practitioner into a false sense of security and this undoubtedly has been the cause of some maternal and many fetal deaths. There are several aspects of this problem which warrant discussion.

1. SAFETY OF MOTHER

In the past five years we have had 28 pregnant diabetic women at the Jewish Hospital. No mothers were lost.

It may be stated that a maternal death from diabetes requires proof that this death was not avoidable. Whereas even in the best of hands such an accident may occur, it should be rare. Joslin has been able to report 73 pregnancies without a maternal death from diabetes, even though 22 of his cases were in total diabetics.

The price for this maternal safety is close collaboration between the obstetrician and the diabetic specialist. Few obstetricians are capable of handling such a problem without help.

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The status of the diabetes changes with the progress of pregnancy and requires constant checking to prevent the development of acidosis and coma. Hyperemesis, with the resultant derangement of metabolism, may tax the skill of the trained diabetic specialist if tragedy is to be avoided. The alimentary and renal glycosuria which are so prone to develop after the middle of pregnancy further complicate the problem. The fetal demands and increased nutritional needs of the end of pregnancy again make control a delicate problem. The old teaching that the development of the fetal pancreas renders the maternal diabetes milder, is not accepted today. Usually the carbohydrate tolerance diminishes as pregnancy progresses. It has been my experience that the insulin requirements increase as pregnancy advances.

2. SAFETY OF BABY

We had four stillbirths in our series. Two of them occurred in cases in which the diabetes was not discovered until glucose tolerance tests were done post partum. One occurred in a case in which the mother refused to follow the outlined therapy. The fourth stillborn infant weighed 11 pounds 15 ounces and died as a result of difficult delivery. Of course, a cesarean should have been performed in this case.

Death of the fetus in utero near the end of pregnancy still occurs occasionally, in spite of all care. Although this accident cannot always be prevented, it is our experience in Brooklyn that vigilance in the care of the mother will reduce its incidence greatly. Hospitalization at the end of pregnancy will undoubtedly prevent many fetal deaths.

3. SIZE OF BABY

Six babies in our series weighed over 9 pounds. The oversized baby of the diabetic woman is well known to obstetricians. It is my opinion that careful control of the diabetes greatly reduces the frequency of large babies. Although there is some difference of opinion, most students of the subject believe that careful control of the diabetes will in most cases insure a live baby of normal size.

It is interesting to speculate here on the cause of this overgrowth of the fetus. The old theory that the overgrowth is due to the abundant food supply (hyperglycemia and lipemia) is now challenged by White. This author believes that it may be caused by the pituitary. The high incidence of toxemia in diabetes, the high prolan in toxemia, and the work of Snyder and Hoopes, who injected prolan into pregnant animals to prolong pregnancy and produce oversized offspring, are neatly joined in a theory to attribute the overgrowth of the fetus to the pituitary. This theory seems plausible, and it will be interesting to see whether further studies bear it out.

4. TOXEMIA

The work of Smith and Smith, who showed high prolan content in toxemias, and the fact that the pituitary is involved in diabetes, make

it likely that the cause of the high incidence of toxemia in diabetic women lies in the pituitary.

5. HYPERINSULINISM OF INFANT

It is believed that the baby borne by the diabetic mother may secrete an increased amount of insulin and this may cause hypoglycemia and convulsions in the first few days of postnatal life. Many authors recommend early feeding of dextrose and even intramuscular injection of 10 per cent glucose to prevent hypoglycemia and its consequences.

6. DELIVERY

Within recent years, several authors have advocated cesarean section before term to prevent death in utero. They advise, when the fetus is sufficiently large, to deliver it by section. Such advice is open to question. I do not believe that the number of babies lost by awaiting labor and delivery warrants this radical step. One author reports that three babies died in a series of 14 patients in whom he performed cesarean section to prevent fetal death. Surely it cannot be pleasant to do a section for a fetal indication and then lose the baby from whatever cause.

In these days, when cesarean section is being done for more and more indications, we should hesitate before adding another indication. Cesarean section is still a dangerous operation and diabetes does not render it less so.

Cesarean section was performed twice in our series. In one case, the indication was cephalopelvic disproportion. In the second case, section was done one month before term because of four previous stillbirths.

It is my opinion that the diabetic patient should be delivered per vagina. If the baby is large and it appears that delivery will be difficult, then cesarean section should be resorted to. In the rare case in which the diabetes cannot be controlled and the condition fluctuates between acidosis and hypoglycemia, section should be done as soon as the fetus is viable and the tubes should be ligated.

Labor must be conducted with extreme care. The diabetic specialist should be in constant attendance. Hourly blood sugar determinations should be made and the urine watched closely for acetone; and treatment should be based upon these findings.

Morphine should be used as an analgesic rather than the barbiturates or rectal ether.

7. THERAPEUTIC ABORTION

Therapeutic abortion was performed four times in our series. In retrospect, the reader believes that this was not always indicated.

Therapeutic abortion is seldom indicated in the diabetic patient today. In the severe case of hyperemesis in which control of the diabetes is impossible, abortion is indicated. There is also the rare case of severe diabetes which becomes worse as pregnancy progresses

and control cannot be maintained. In this case, termination of pregnancy is indicated to save the mother's life. Fortunately, this is seldom necessary.

8. ANESTHESIA

For delivery per vaginam, local infiltration or pudendal block is the anesthesia of choice. For cesarean section, local infiltration is safer than general or spinal anesthesia.

9. CONCLUSIONS

1. Death of the fetus near term can usually be prevented.
2. Adequate care will usually prevent an oversized baby.
3. Death of the mother should be rare.
4. Cesarean section is warranted only for special indications.
5. Therapeutic abortion is seldom indicated.

652 EASTERN PARKWAY

BILATERAL SIMULTANEOUS TUBAL PREGNANCY

HAMILTON R. FISHBACK, SC.D., M.D., CHICAGO, ILL.
(From the Department of Pathology, Northwestern University Medical School)

A REVIEW of bilateral simultaneous tubal pregnancy cases uncovers a number with insufficient data for classification. Aside from the clinical facts given in reports there should be a description of the fetuses or any portion of them found, as well as of placental material. A microscopic examination may be necessary to confirm the diagnosis and to give criteria for fixing the pregnancy periods. Especially is this needed where only a hematosalpinx is present grossly. Fetal structures recently dead may give dependable findings,[1] but badly degenerated tissues or mummified or calcified products are of little value in estimating the time factor.

Many of the cases were found in journals of limited circulation, and probably others have been missed because of inaccessibility. Those presented in earlier reviews have been gone over with the above criteria in mind and acceptable ones are included here.

The review by Jayle and Nandrot (1904)[2] includes two acceptable cases, one each of Johnson, and of Jayle and Nandrot. Labhardt (1909)[3] adds seven more cases. Five new cases are added by Launay and Seguinot (1911),[4] and two by Unterberger (1913).[5] The subject was considered at length by Bledsoe (1918)[6] with the presentation of 24 new actual or highly probable cases. Borell (1921)[7] found 9 more. A thesis by Bloch (1931)[8] presents 11 additional cases. Another case, the third case of Penot, is found in the review of von Kupereyn (1932).[9]

Other cases, not discussed in the foregoing reviews, will be named here without discussion. Lockyer (1916),[10] Jordan and Bigger (1925),[11] Dalzell (1927),[12] Schockaert (1928),[13] two cases of Nevinny (1929),[14] Heymann (1932),[15] Johnston (1932),[16] Cramarossa (1934),[17] Stahel (1934),[18] Langley (1934),[19] Léon-Borcéa (1935),[20] Siegler (1935),[21] Corceovei and Corceovei (1935),[22] and Muller (1935).[23]

The entire group represents 76 cases of bilateral simultaneous tubal pregnancy, reviewed in the light of the principles for acceptance discussed earlier. To these I should like to add a further case. This patient was proved to have 3 simultaneous tubal pregnancies, 2 in the left and 1 in the right tube. Only 2 similar cases have been found reported previously, 1 by Launay and Seguinot (1911),[4] and the second by Baldwin (1913).[24]

CASE REPORT

Patient H. C., aged 32 years. In seven years increased from 145 to 227 pounds in body weight. She was married and had had three spontaneous abortions; no living children. Menses were regular and normal except during her pregnancies. Last regular period was twelve weeks before entry into hospital. Almost daily spotting for the last four weeks, and for two weeks this was accompanied by vague lower abdominal pains. On the day of entrance, she was seized with sudden sharp cramplike pains in the lower abdomen, and shortly thereafter passed a small amount of blood vaginally. Several hours later she had a second attack of similar acute abdominal pain and was brought to the hospital in a shocklike state and was operated upon.

A massive hemorrhage was found in the peritoneal cavity. The left tube was much enlarged near the middle, ruptured, and bleeding. The right tube had three soft swellings. Both tubes were removed. The patient died five days after operation. Post mortem was refused.

Pathologic Examination.—The left tube measured 11 cm. in length. The distal 3½ cm. was slightly swollen, 10 to 12 mm. in diameter, pink and soft. The fimbriae were blue red, slightly swollen and freely separate. The ostium was open, and the lumen patent in the smaller distal portion. The remainder of the tube was made up

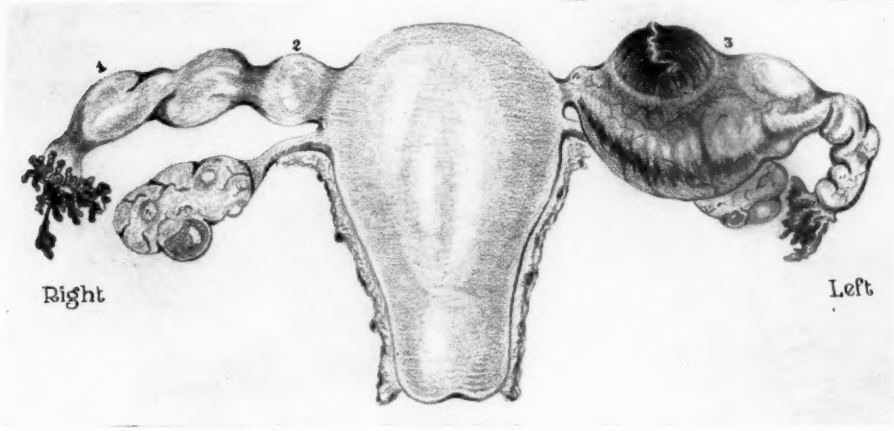

Fig. 1.—Multiple tubal pregnancies, showing sites at *1*, *2*, and *3*.

of a fusiform swelling 5 cm. in its greatest diameter, and blue red in color. A slightly raised darker red area 3 cm. in diameter had a ragged tear across it. On opening the tube, the dilated portion was filled with dark red solid blood clot. No remnants of sac nor embryo could be found, and placental strands were difficult to verify because of the extensive, rather dry clot.

The right tube was 9 cm. in length, pink red, soft and swollen throughout. The fimbriae resembled those of the left tube. A small blood clot dilated the distal end slightly, with strands of clot extending through the ostium. A sacculated swelling occupied approximately each third of the tubal length. Each saccule was 2 cm. in largest diameter, and on opening was filled with dark red soft blood clot.

Microscopic sections of the tubes demonstrated chorionic villi attached to the walls and free in the blood clot of the lumen at the three sites numbered in the drawing. The villi were of similar developmental stage. No remnants of the embryos proper were found.

SUMMARY

Attention is called to some points of difficulty in verifying reported cases of multiple simultaneous tubal pregnancy. The few requirements for acceptance of cases

are stated. The source material of 76 verifiable cases is given. A third case is presented of simultaneous twin pregnancy in one tube and a single pregnancy in the other tube.

Acknowledgment is made here to Dr. J. V. Fowler who kindly permitted use of the clinical material of this case.

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MANAGEMENT OF AN INSTITUTIONAL OUTBREAK OF INFECTIOUS DIARRHEA OF THE NEWBORN INFANT*

Rudolf L. Roddy, M.D., James S. Forrester, M.D., and Harold Landow, M.D., Philadelphia, Pa.

(From the Department of Pediatrics, University of Pennsylvania Hospital, and the William Pepper Laboratory of Clinical Medicine)

Infectious diarrhea of the newborn infant, of undiscovered etiology, often carrying a high mortality rate and occurring usually as a localized outbreak among a hospital's newborn population, has recently attracted considerable attention.[1] The outbreak here reported follows closely the recorded descriptions of this condition, with the exceptions that no deaths occurred, and that the outbreak was controlled in the hospital without the interruption of the maternity and newborn nursery services. Best[2] has advocated closure of these services for the duration of the epidemic.

The newborn nursery of the University Hospital is equipped to accommodate 48 infants, with separate but adjoining rooms for premature and full-term infants, and a common nursing and professional personnel. An additional room is provided for isolation of infectious cases.

The outbreak began Sept. 8, 1937, in the nursery for prematures, with repeated vomiting and passage of loose stools by a single infant. The nature of the illness was not immediately recognized and infec-

*Read at a meeting of the Philadelphia Obstetrical Society, October 6, 1938.

tious precautions not at once established. By September 10, extreme dehydration was apparent, 6 large liquid stools having been passed in the previous twenty-four hours. On this date, the 5 other infants in this nursery began to be affected, with passage of frequent loose or watery stools. Isolation of the entire premature nursery was then established, but during the following several days new cases began to appear in the adjacent full-term nursery, eventually affecting 14 of the 28 occupants of the two nurseries. All 6 of the premature group and 8 of the 22 full-term infants were involved. Distinction between breast- and bottle-fed infants was difficult to make, as all were receiving as supplementary feeding a 5 per cent glucose solution. Ten of the sick infants, however, were classed as "artificially fed," and 4 as "breast-fed."

CLINICAL DESCRIPTION

The clinical picture resembled in all respects that described in previously reported outbreaks, except that it was in general less severe. The most constant and notable feature was the passage of frequent loose or watery stools which contained no blood, pus, or mucus, the daily frequency varying from 3 to 8. Weight loss varied from 3 to 13 per cent. Dehydration, rapid in onset and of severe degree, was the outstanding symptom in 8 cases; 2 others were mildly dehydrated. In 3 cases clinical acidosis was evidenced by Kussmaul respirations. Elevation of temperature was in no case marked or prolonged but 4 babies had a low grade fever, in one case associated with an intercurrent upper respiratory tract infection, and in another, following a blood transfusion. Vomiting was limited to 4 cases, and was not a prominent feature in any case; it usually occurred at the onset of the illness. Laboratory studies revealed leucocyte counts of from 11,000 to 14,500 per c. mm.; hemoglobin values varied from 12.5 gm. to 17.8 gm. per 100 c.c.

BACTERIOLOGY

Bacteriologic studies included stool cultures of sick and well infants, throat cultures of infants and mothers, urine cultures of mothers, and throat cultures of the nursing and professional staff as well as a survey of the formula preparation technique.

Stool cultures were plated on blood agar, Endo's medium and bromthymol blue-lactose agar, or eosin methylene blue-lactose agar. On these media cultures were uniformly negative for members of the typhoid, Salmonella and dysentery groups. The predominating organism from the stools of 20 sick and well infants was a late lactose-fermenting colon bacillus. Though Fothergill[3] and associates attribute considerable significance to the finding of such organisms in outbreaks of infantile diarrhea, its presence in this series was considerably discounted because of its recovery from well infants who did not develop diarrhea.

Throat cultures of sick and well infants showed no predominating or uniformly present organism. *B. coli* was recovered from 4 infants, hemolytic streptococcus from 2 cases. Throat culture from mothers on the ward showed only the usual flora except for 2 of the mothers who delivered after the outbreak had begun. In both these cases, hemolytic streptococci were recovered.

Urine cultures from the mothers of sick infants showed a variety of organisms, most commonly *B. coli*. From the urine of one patient's mother who delivered well after the outbreak of the disease, an organism was recovered with the biologic characteristics of members of the Salmonella group. It was partially agglutinated by paratyphoid A antiserum. This organism was not recovered from any other source and was not agglutinated by any of the sera of 12 convalescent infants, taken at periods of ten to twenty days after onset of illness. Serum agglutination studies were also carried out against staphylococcus and *Shigella paradysenteriae*, Flexner, Hiss, and Sonne. In no case was any agglutination observed.

Bacteriologic investigation of the formula preparation technique included culture of the formula, nurse's hands, throat and mask, and culture of sterilized utensils and receptacles as well as the unheated ingredients of the formula. The only suggestive finding in this study was the recovery of *B. coli* from 1 of 8 "sterile" empty formula bottles. Throat cultures from members of the professional staff showed no significant flora.

MANAGEMENT

Because of the apparent relative mildness of the disease from the outset, it was decided that, rather than temporarily closing the maternity service, the attempt would be made to control the outbreak by rigidly isolating all cases and contacts. In order to avoid the mingling of newborn susceptibles with "exposed" infants, three nurseries were established; in one, sick infants were lodged; in a second, well contacts were placed; in the third room, previously not used for that purpose, an emergency nursery for newborn noncontacts was established. The distribution of the Maternity Service at the University Hospital on 3 floors enabled us to obviate completely the possibility of chance contacts. The ill children were housed on the fourth floor, in a room adjacent to the "septic" maternity cases. "Contact" infants were held in the hospital only for the necessary maternal post-partum period, and then discharged to their homes, where follow-up visits were made by a social service worker to discover any newly developing cases. None developed, however. Cases in the "sick" nursery were discharged when diarrhea had ceased and they were able to tolerate ordinary milk mixtures.

The nursing service in each of these nurseries was completely separated from the other two, the only common service being the formula preparation. Strict aseptic precautions by the nursing staff between well but "exposed" infants was found impracticable, but cribs were separated as well as possible and nurses instructed to wash their hands thoroughly after changing or feeding each infant. As soon as the regular ("contact") nursery was emptied by discharge or transfer, it was thoroughly scrubbed and aired, and the unexposed newborn infants transferred to it from the "emergency" nursery.

THERAPY

The sick infants were given 1:10 powdered protein milk, followed by skimmed lactic milk and 2 per cent milk as tolerated. Dehydration was combated by the subcutaneous injection of lactate-Ringer's solution; acidosis was controlled by intravenous and subcutaneous sodium lactate. Transfusion of citrated blood was employed for 3 premature infants with general debility and extreme dehydration.

All of the sick infants recovered. On follow-up one proved to have continued to pass loose stools for a week after discharge. Another who did not return for follow-up, continued to have loose stools for three months. The others remained symptom-free. It is interesting to note that none of the "contacts" developed diarrhea after discharge. None of the infants born after establishment of the emergency nursery became ill.

COMMENT

In most essential aspects, the outbreak here reported resembles those previously described as "infectious diarrhea of the newborn," the outstanding features being frequent, watery stools, rapid dehydration, afebrile course, high morbidity, and inability to demonstrate an etiologic agent, in spite of intensive bacteriologic study. The absence of mortality is, however, in contrast with the usual high percentage of deaths reported, although it is not unique.[1]

SUMMARY

An outbreak of infectious diarrhea of undiscovered etiology, affecting 14 of 28 infants in a hospital nursery for the newborn, is reported.

No deaths occurred. A method of management is described, by which the addition of new susceptibles to the infected group is avoided, without interruption of the maternity service.

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DISCUSSION

DR. THEODORE S. WILDER.—It is perhaps appropriate here to mention two small epidemics among the newborn babies at the Germantown Hospital, which appear to resemble in all respects the epidemic Dr. Roddy has described.

The first occurred in September, 1937, affecting 5 premature infants only, and was characterized by sudden onset with vomiting, and by 12 to 15 watery, yellow or green stools daily, which were free from blood or mucus. Dehydration was extreme, and was accompanied by cyanosis, which disappeared on administration of subcutaneous fluids. These infants all recovered within three weeks, thanks largely to the use of glucose and salt or lactate solutions under the skin, thrice daily.

A year later, almost to the day, a second outbreak occurred, clinically identical with the first. This involved 11 infants; treatment was the same, and there were three deaths. But of the deaths one was a premature infant, and the other two were babies who, discharged at fourteen days, apparently well, promptly developed enteritis at home, and were readmitted to the ward several days later, in a moribund condition.

Bacteriologic search for a causative organism revealed a motile, nonlactose fermenting, gram-negative bacillus in all 9 of the infants whose stools were cultured. This organism was agglutinated by the serum of one of the patients a month later in 1:200 dilution, and is being studied further.

A feature of both outbreaks at the Germantown Hospital was the fact that all the cases occurred within a few days of each other, as though there had been a sudden exposure, following which there were no secondary cases. Whether cessation of the epidemic was due to precautions taken, or to the fact that the infectious source no longer was operative one cannot say. The results, however, justified our not closing the maternity service, as has been advocated in connection with similar, but perhaps more severe, epidemics in New York Hospitals.

DR. OWEN J. TOLAND.—I have recently read an article from New York which states that once a diagnosis of epidemic diarrhea has been established in a maternity nursery, the only thing to do is to discontinue completely the maternity service. I have also seen recently an article which, in view of spreading epidemics, advised that the only thing to do was to re-educate the public to have their babies at home.

Bertolotto, U.: Short Wave Therapy to the Hypophysis in Certain Forms of Metrorrhagia, Folia Gynaecologica **25:** 377, 1938.

The author reports upon a new method of therapy for various forms of metrorrhagia by the use of short wave treatment applied to the hypophysis. He discusses the genesis of certain types of bleeding, outlines his method of experimentation, form of application and technic. Based on his experimental research he explains the mode of action of short waves and enumerates the advantages which this method of treatment presents in various forms of bleeding, both in gynecology and obstetrics.

MARIO A. CASTALLO.

AN UNUSUAL CASE OF CHRONIC INVERSION OF THE UTERUS*

HARRY ARANOW, M.D., NEW YORK, N. Y.

CHRONIC inversion of the uterus per se is sufficiently rare to make it worth while reporting every case and what makes my case still more unusual is the fact that the inversion involved not only the body of the uterus but also the cervix including the portio vaginalis (Fig. 1). In a rather superficial examination of the literature I have been unable to find a report of a similar case.

CASE REPORT

M. S., white, housewife, aged 24 years, married 5 years, was born in New York. No operations. Menstruation began at 12, every thirty-five days, periods lasting two days, scant in amount and without pain. Sexual life apparently normal. Took contraceptive precautions for four years.

Her last period was on June 30, 1935. Expected date of confinement April 7, 1936. She had a normal pregnancy.

Patient began to have irregular pains on April 8, 1936. On April 9 she was admitted to a private hospital. After twelve hours the patient was sent home. She continued to have irregular pains for ten days. At about 11 P.M. on April 19 the bag of waters ruptured, and the patient was apparently about to deliver. She was rushed to the hospital, and the baby was born spontaneously. The placenta was delivered with difficulty, i.e. there was considerable pressure necessary to deliver it. This took place about twenty minutes after the birth of the baby.

The delivery was followed by a severe post-partum hemorrhage which the family physician was unable to control. The patient repeatedly bled through the packing in the vagina. One of my associates who was called in consultation told me that he thought the patient had a cervical tear but that she bled so furiously and was in such bad shape that he could not attempt a repair. She was packed and repacked. She received a transfusion at 1:50 A.M. and another at 3:30. The bleeding was finally controlled the following day. The anemia and shock were treated by transfusions, infusions, liver, iron, etc.

During her post-partum period the patient complained of severe backache and inability to move her legs. She had a peroneal paralysis of both legs with foot drop. She remained at the hospital for a fortnight and was taken home in an ambulance. At home she was bedridden because of the paralysis and there was continuous vaginal spotting.

On June 5, 1936, she had a sudden severe vaginal hemorrhage and was brought to the Morrisania Hospital much exsanguinated. The condition was readily diagnosed. There was a firm bleeding mass the size and shape of an inverted pear filling the vagina, and a bimanual examination revealed the absence of a uterus above the vaginal vault.

The vagina was packed and the patient was given a transfusion. The packing had to be replaced several times because of saturation. On June 8 an attempt at a careful examination for the purpose of deciding the best method of treatment was accompanied by such severe hemorrhage that it had to be abandoned. However, we obtained sufficient information to make us feel that a vaginal operation was indicated as soon as the patient's condition permitted. In the meantime the patient's condition continued to be rather serious. Her pulse was rapid and weak and she continued to bleed through the packing. On the night of June 9 she began to bleed profusely and her general condition grew rapidly worse. However, we felt that

*Presented at a meeting of the New York Obstetrical Society, November 8, 1938.

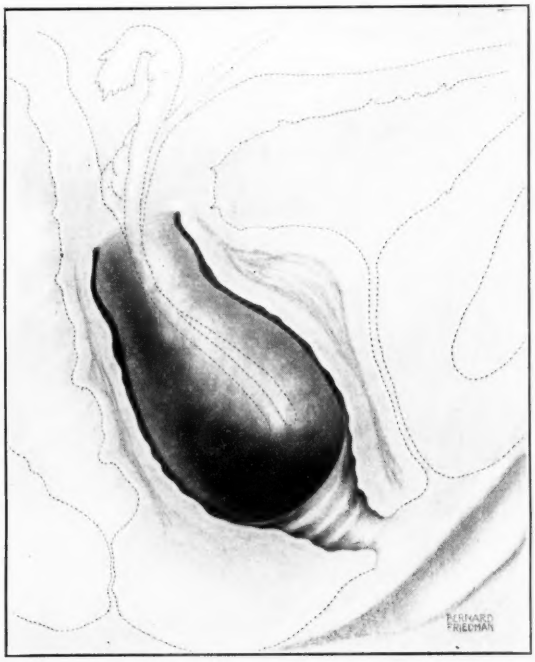

Fig. 1.—Complete uterine inversion including vaginal portion of cervix.

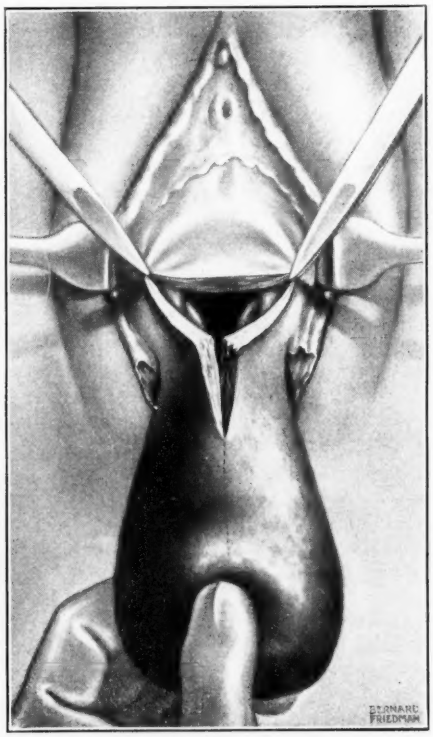

Fig. 2.—Showing transverse incision above edge of cervix, bladder pushed up, and peritoneal cavity opened.

under the circumstances a hysterectomy would be fatal and suggested an exposure of the inverted uterus, controlling the bleeding points with the coagulation cautery to be followed by another transfusion.

The patient reacted so favorably to the above treatment that on June 13 she was prepared for a vaginal replacement according to the Spinelli method.

At the operation, when the vagina was retracted and the inverted uterus exposed, I was greatly surprised to find that there was no cervical cuff. Apparently the inversion had proceeded and involved the entire cervix, including the portio vaginalis. At the base of the inversion the mucous membrane of the uterus was continuous with the mucous membrane of the vagina without a ridge or scar. This necessitated a slight change in the technique of the operation.

The tip of the inverted cervix was identified by palpation and a transverse incision was made in the mucous membrane of the vagina just above it. With a sound in the bladder, the bladder wall was exposed and separated from the anterior wall of the cervix and vagina. The vesicouterine fold of peritoneum was opened, exposing the edge of the cervix and the inversion funnell (Fig. 2). An incision was made from the cervix to a little beyond the apex of the fundus and the uterus turned "inside-in" without difficulty. Here another unexpected situation awaited us. In our efforts to control the bleeding we had coagulated the greater portion of the anterior wall of the uterus. The tissues were gray and bloodless. We were extremely reluctant to sacrifice the uterus in such a young woman and so we excised the dead parts of the anterior wall of the uterus and brought the healthy raw edges together by layers of chromic catgut. Tubes and ovaries were found normal. A rubber tube drain was placed in the cul-de-sac through a stab wound and another into the vesicouterine space. Peritoneum, fascia, and mucous membrane were sutured with chromic catgut.

The perineum which had been lacerated during the delivery and subsequent manipulations was repaired. The patient made an uneventful recovery.

During her convalescence the neurologic and orthopedic departments of our hospital helped us take care of the paralysis, and on July 5 exactly a month after her admission the patient walked out of the hospital a well woman.

For about a year the patient did not menstruate but had no signs of menopause. Just as we were about to make a hormonal study of the blood and urine, the patient had a normal menstruation. She has menstruated regularly since. A follow-up note by my resident on Dec. 17, 1937, reads as follows: "Menses regular, no leucorrhea, excellent anatomic result."

DISCUSSION

DR. ONSLOW A. GORDON.—In 1934 I reported a series of 7 cases of inversion of the uterus, all operated upon without mortality. One patient in the series, who had a Spinelli operation, died two years later following rupture of the uterus, occurring before the onset of labor. One must bear in mind that when the Spinelli operation is done, subsequent pregnancies are a dangerous complication.

I believe that the abdominal operation devised by James Huntington, of Boston, would have been particularly apropos in Dr. Aranow's case, for there was no apparent cervical constriction. It is the cervical constriction in chronic inversion which is the difficult factor in reduction of the inversion. Masson, however, reported a series of patients with chronic inversion operated upon abdominally in which there was marked cervical constriction. He incised the cervix in the midline, posteriorly, and, thus, easily reduced the inverted corpus abdominally.

The advantages of the abdominal operation are: The exposure is much better. There is usually much less bleeding. There is less trauma to the body of the uterus. The woman is left in a much safer condition for subsequent pregnancy. Should hysterectomy be necessary it may be more readily done either before or after reduction of the inversion.

DR. DAVID NYE BARROWS.—About six years ago I reported before this Society a similar case of complete inversion operated upon abdominally. The procedure was extremely simple as the cervix had risen nearly to the pelvic brim and an incision through the posterior lip into the vaginal vault made it easy to split the

posterior uterine wall, and reinvert the uterus. That patient was advised not to become pregnant for five years, but after four years she conceived. An elective cesarean section was done, and the old scar found to have healed perfectly.

DR. EDWIN W. HOLLADAY.—Having noticed the technical difficulties in two Spinelli operations and the simplicity of the abdominal operation, I wish to corroborate what Dr. Barrows has said as to the superiority of the abdominal approach. I believe Dr. Aranow would have found this so in his case.

The technique is very simple. With the operator working through the abdominal wound, he can dilate the constricting ring or cut it posteriorly. A third assistant, with a hand in the vagina, pushes up the inverted uterus to the vault of the vagina. The operator can now seize in the hollow of his hand the still inverted uterus. By kneading with the tips of his fingers and with gentle traction, he will be amazed to see the uterus practically correct its position itself.

DR. F. A. WURZBACH, JR.—To stop the bleeding in this case I had to cauterize the anterior surface of the uterus. In cases that do not have the rough treatment to which I had to subject this uterus I do not doubt that the abdominal operation would be better. This patient, however, was in pretty bad condition and undoubtedly the peritoneal cavity would have become infected.

DR. EDWARD G. WATERS.—I think it may be worth while to comment on the advisability of doing a vaginal examination on bleeding patients post partum and before discharge from the hospital. There are three things that cause a woman to bleed immediately post partum: cervical lacerations, rupture of the uterus, and inversion of the uterus. There is no way of telling which of the latter two may be present except by an adequate vaginal examination in the presence of bleeding that is demonstrated as not coming from the cervix.

We have seen five cases at Margaret Hague Maternity, and one fatality occurred where the inversion was not recognized. The other four were immediately replaced and then shock treatment was instituted. The response of the patients was so good that one or two days later you would not know that anything serious had happened.

DR. ELIOT BISHOP.—Cases of inversion of the uterus must be placed in two categories: One as to time—is it acute or chronic? the other as to the physical state—is the patient infected or in shock?

If the case is in the first category, and inversion has just occurred, immediate laparotomy, with presumably a transfusion, and traction from above according to the method published by Huntington, Irving and Kellogg some years ago, ought to bring cures with a low mortality and morbidity. If the case is in the first category, but not infected or shocked, an elective Spinelli operation should be the choice, for, thus, the inversion can be reduced with no loss of organs.

If the case is in the second category and is infected, but not in shock or with hemorrhage, she must be treated for infection, in any way that seems best suited. If shock and hemorrhage exist, treatment should be directed toward them; transfusion should be given, and it would seem to me that the suggestion of the reader of the paper, local cauterization, deep suturing and firm packing, are the first methods of attack.

DR. ARANOW (closing).—We are allowed to do vaginal work only on our service at the Morrisania Hospital. As a result I have learned to prefer vaginal work. I find the vaginal route just as easy and a little safer. In this particular case the abdominal route was considered but because of the marked edema of the endometrium, a simple reduction of the inversion without extensive incision of the corpus uteri seemed impossible.

A MODIFIED STURMDORF OPERATION FOR VESICOVAGINAL FISTULA*

ABRAHAM KOPLOWITZ, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Gynecology and Obstetrics, Beth-El Hospital)

WITH better training in the use of the prophylactic forceps and episiotomy, and the practical elimination of the midwife, vesicovaginal fistula due to poor obstetrics has almost disappeared.

A great number of the fistulas seen today are due to radium used in the treatment of carcinoma of the uterus. Improved technique and the greater use of the x-ray are diminishing that as a source. An occasional case, however, is still seen and the problems of its repair still exist.

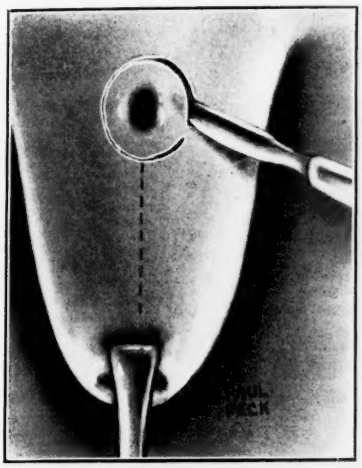

Fig. 1.

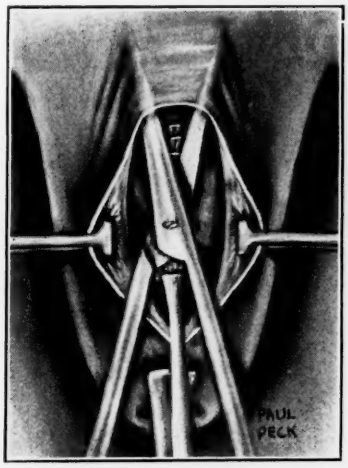

Fig. 2.

Fig. 1.—Incision of vaginal mucosa around fistula about one-fourth of an inch from edge which is freed and then used to close fistula. Incision in midline below this to reflect flaps to side shown by dotted line.

Fig. 2.—Flaps reflected to side and blunt scissors dissecting vaginal mucosa from bladder above fistula.

From the time of Marion Sims there have been innumerable modifications of the operation for the cure of fistula and one hesitates to add anything to the voluminous literature on the subject.

In addition to the three cardinal postulates of Sims, that is, proper exposure; a reliable suture and an empty bladder; it seems that a fourth, though mentioned by different writers, might be emphasized, namely, the suturing of the bladder and vaginal walls in different planes.

In the technique described below two ideas were utilized which seem to insure success in the great majority of vesicovaginal fistulas situated in the upper two-thirds of the anterior vaginal wall. In 1919 George Gray Ward described his operation for cystocele and coined the word "cystopexy" for part of his technique. He did this by freeing the bladder from its cervical attachment, reflecting it upward by blunt dissection, revolving it on its transverse axis, and suturing it to the uterus somewhat above the internal os. In 1925 Sturmdorf described the use of his "cuff"

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in the cure of a fistula which was operated on 5 times unsuccessfully. He prepared his "cuff," as in his well known tracheloplasty, except that he slit on both sides for greater mobility, had no trouble in thus separating the anterior vaginal wall from the bladder, repaired the defect in the latter and brought the "cuff" down and inverted it into the coned out cervix. He thus obtained the advantage of bringing an intact vaginal wall over the sutured bladder, but his method is only possible where the fistula is very low for obvious reasons.

It occurred to me that the utilization of the cystopexy with an intact vaginal wall over it would insure a perfect healing; the following case, with technique used therein, is therefore reported.

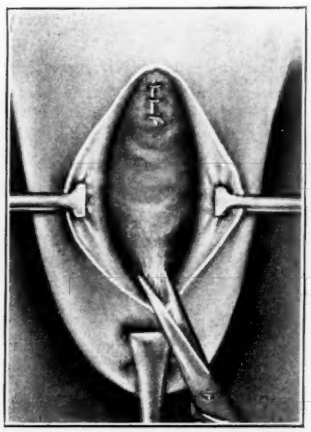

Fig. 3.

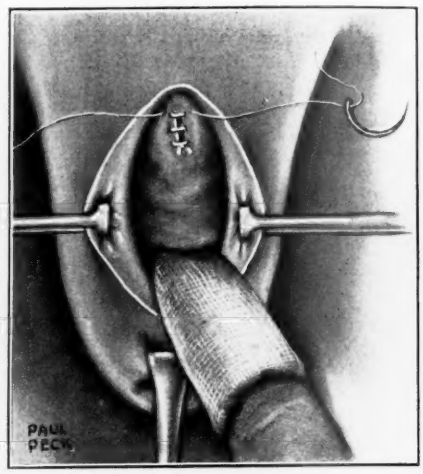

Fig. 4.

Fig. 3.—Vaginal flaps retracted to sides, vaginal mucosa above fistula separated from bladder as in Fig. 2, and uterovesical ligament severed.

Fig. 4.—Suture of chromic No. 2 inserted in bladder above fistula and blunt dissection of bladder begun.

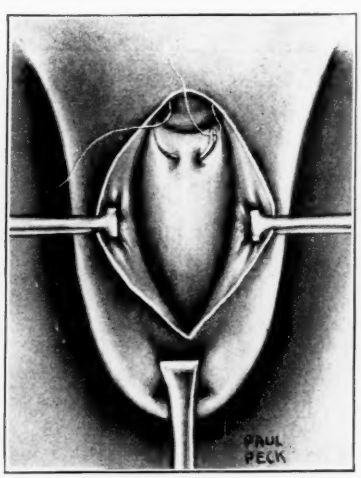

Fig. 5.

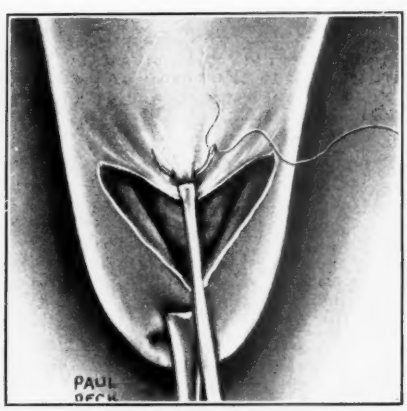

Fig. 6.

Fig. 5.—Upper suture taking bite in uterus somewhat above internal os which will revolve bladder transversely.

Fig. 6.—Upper part of freed vaginal mucosa brought down and sutured below attachment of bladder.

Mrs. H. B., 27 years of age, married four years, was admitted to Beth-El Hospital, Apr. 27, 1934. Previous history irrelevant. She was delivered in January, 1934, after a prolonged labor, with midforceps, of a living child which died four weeks later of congenital heart disease. Patient began to dribble urine the day after delivery and continued until present admission. Condition on admission was excellent except for complete loss of urine from a vesicovaginal fistula situated about midway between urethra and external os, measuring about 2 cm. in length and somewhat less than a centimeter in width. Except for the scars around the fistula, the parts were in good condition and practically ready for repair.

The technique used was as follows (Figs. 1 to 7): An incision in the vaginal mucosa around the fistula about a fourth of an inch from its edge was made, and the flap freed, and used to help close the fistula. An incision in the vaginal wall in the midline below this was made and the two flaps freed laterally for some distance, then upward around fistulous opening and above it for about an inch and a quarter, freeing the vaginal wall from the bladder by blunt dissection while

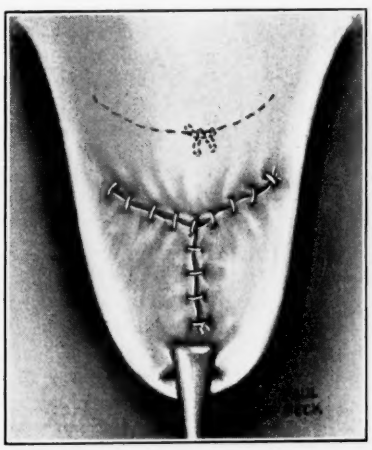

Fig. 7.—Operation completed, showing vaginal closure some distance below bladder attachment.

the latter was held taut by an Allis clamp. The vesicocervical ligament was then severed and the bladder bluntly dissected upward to beyond the internal os. A cystopexy was then done as described by Ward, taking a bite in the bladder at the upper edge of repaired fistula and suturing it to body of the uterus above the internal os. The upper edge of vaginal mucosa was then brought down and sutured to the uterus below the new attachment of the bladder, thus giving the fistula a wall of uterus posteriorly, in addition to its own closure and an intact vaginal mucosa over it. The original lower flaps were then sutured partly transversely to take up the slack by having brought the upper flap down. An indwelling catheter was left in the bladder for seven days. The bladder was washed twice daily with 1 per cent phosphoric acid to prevent encrustations.

I do not offer this technique as a method for every kind of fistula. Many defects are so situated that different methods of approach will be necessary, but the principle of closing the bladder and vaginal openings in different planes will add much to the success of any operation for fistula.

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1401 President Street

IMPLANTATION OF OVARY IN THE UTERINE CORNU*

MARGARET CASTEX STURGIS, M.D., F.A.C.S., PHILADELPHIA, PA.
(From the Department of Gynecology of the Woman's Medical College of Pennsylvania)

WHILE the implantation of an ovary or part of an ovary in the uterine cornu is not new, it still is not a common surgical procedure. The results in this particular case justify the plea for more conservative ovarian surgery in young women suffering with complicated chronic pelvic inflammatory disease in which the whole of both tubes and one ovary or even one ovary and part of the other must be removed.

This patient, a colored woman twenty-seven years of age, married eleven years, was first seen in December, 1931. She was admitted to the Clinic of the Hospital of the Woman's Medical College, seeking relief from constant backache, pelvic pain, and discomfort. She gave a history of three abortions early in her married life, reported as spontaneous and of about three months' duration. Five months previous to admission she had had an attack of pelvic inflammation, and at the time of admission to the hospital, pelvic examination revealed an adherent retroverted uterus with bilateral tender adnexal masses. Sedimentation rate was sixty minutes and Wassermann was negative.

The patient was operated upon Jan. 2, 1932. Bilateral pyosalpinx with inflammatory adhesions, oophoritis, and adherent retroverted uterus were found. It was necessary to remove both tubes and all of the right and part of the left ovary. The left ovary was resected, preserving intact the utero-ovarian ligament with its small blood vessel and nerve supply, and was implanted in the left cornu after a wedge-shaped removal of the cornu had been made. The cut surface of the ovarian cortex was implanted on the uterus over the tubal opening and the intra-abdominal surface was peritonized. The round ligaments were plicated and sutured to the post surface of the uterus after the Estes method, covering both uterine horns. This shortening of the round ligaments likewise secured the anterior position of the uterine body. The uterus was normal in size and without demonstrable pathology. The patient made an uneventful recovery and continued the menstrual function as usual. In September, 1932, Dr. Virginia Alexander, her private physician, reported that the patient was pregnant. Unfortunately, however, the patient aborted a three and one-half months' fetus on Oct. 16, 1932.

The patient was not seen again until February, 1938, when she gave a history of having been perfectly well until October, 1937, when she again began to suffer with lower abdominal pains and backache. The periods prior to this time had been regular, twenty-eight-day interval and five days' duration, amount moderate. October, November, and December periods had a longer interval, were irregular, duration more prolonged and flow scanty. The last menstrual period was Dec. 29, 1937. There was no January period so the increasing backache and pelvic discomfort brought the patient to the hospital.

Examination revealed a firm, irregular enlargement of the uterus. A diagnosis was made of multinodular uterine myoma. A pregnancy test was negative so the patient was operated upon Feb. 10, 1938. A multinodular myoma involving the entire uterine body was found with the small amount of ovarian tissue at the left cornu to which were omental adhesions. There were no other adhesions in the pelvis. The omentum was ligated and the attachment to the ovary incised and a supravaginal hysterectomy was done. The patient made an uneventful recovery.

This case is important in that pregnancy did occur; hence there was restoration of the "opportunity" for pregnancy.

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The second important result and that of prime importance was the maintenance of a normal menses for six years. The atrophy of the ovary as recognized on microscopic section and evidenced clinically by dysfunction during the last three months, could be explained as being hastened by the interference in the blood supply by the fibroid growth in the uterus.

This case does not present the objections to this operation sometimes advanced. There had been no pain experienced at the ovarian site. The ovary had not become cystic and the atrophy had not commenced early.

The operation for the removal of the myomatous uterus permitted the study of the anatomic and histologic end results following an ovarian transplant into the uterine cornu.

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1950 Chestnut Street

MASSIVE INTRAPERITONEAL HEMORRHAGE RESULTING FROM RUPTURE OF A SUPERFICIAL VEIN OF A UTERINE FIBROMYOMA*

Anthony L. Shelfo, M.D., Brooklyn, N. Y.

(From Kings County Hospital, Long Island College of Medicine Division)

RUPTURE of a vessel situated on the surface of a uterine fibroid is an extremely rare condition as evidenced by the few reported cases in the literature. The vessel usually involved is a vein running between the capsule of the fibroid and the peritoneum.

Most writers in discussing complications of fibromyomas fail to mention this condition. Reference to it has been in the form of case reports.

The two cases about to be reported bring the total number in the literature to 48.

They are reported because of their rarity, their gravity, and the problems they offer in differential diagnosis from such conditions as ruptured ectopic pregnancy, ruptured corpus lutein cyst with hemorrhage, or torsion of an adnexal tumor.

CASE REPORT

L. G., aged 52, colored, married, gravida xiii, para ii, was admitted to Kings County Hospital on April 19, 1936, in shock. Her last period occurred two weeks before admission to the hospital. The patient was well until eight o'clock in the morning of admission when she was seized with a sharp lower abdominal pain which caused her to collapse. The pain persisted and her condition grew rapidly worse.

On admission she had a blood pressure of 50 systolic and zero diastolic, pulse 84 and feeble, temperature 100.8° F. The skin was cold and clammy. Abdominal examination revealed a tender, firm, ballotable mass in the lower mid-abdomen the size of a large grapefruit. Vaginal examination showed the mucous membrane to be pale in color. The cervix was tender to motion and continuous with it was the mass felt in the abdomen.

White blood cells 9,200, with 62 per cent polymorph leucocytes and 38 per cent lymphocytes; red blood cells 4,200,000, hemoglobin (Sahli) 80 per cent. Urine showed two-plus albumin and otherwise was negative.

*Read at a meeting of The Brooklyn Gynecological Society, December 2, 1938.

A preoperative diagnosis of intra-abdominal hemorrhage from unknown origin associated with a fibroid uterus was made. The patient was given a preliminary transfusion of 500 c.c. of whole blood and then a laparotomy was done. The peritoneal cavity contained at least one quart of free blood and clots. The uterus was slightly enlarged, firm in consistency, anterior and mobile. Arising from the posterior fundal region was a large sessile fibroid measuring 7 by 5 inches whose lateral aspect presented many dilated varicose veins. One of the larger varicosities had ruptured and at this site was covered with a clot. When this was dislodged active bleeding ensued. A supracervical hysterectomy was performed. The postoperative course was uneventful and the patient was discharged on the fifteenth day in good condition.

The second case presented a similar clinical picture, and profiting by the previous case, the condition was considered preoperatively.

N. H., aged 31, colored, married, was admitted to Kings County Hospital, Service of Dr. Charles Gordon, on Aug. 3, 1937, at 1:10 P.M. in a state of collapse. The history obtained was of no help except to elicit that there had been no pregnancies and that her menses had been regular. The last period occurred in July.

The patient was well until eleven o'clock the morning of admission when she experienced a sudden, persistent, sharp pain in the right lower quadrant of the abdomen. This weakened her considerably, hence she sought hospitalization and was admitted via ambulance.

On admission the blood pressure was 56 systolic and zero diastolic, temperature 99.2°, pulse 88, feeble and inconstant, respirations 26. The patient was restless and apprehensive, skin cold and clammy. The abdomen was soft and tender over the right lower quadrant where a firm mass the size of a large orange could be felt. Vaginal examination revealed the cervix tender to motion and a mass in the left fornix which was firm in consistency, the size of a hen's egg. The abdominal mass could not be felt through the vagina.

White blood cells 9,000, with 69 per cent polymorph leucocytes and 31 lymphocytes; red blood cells 3,900,000, with 78 per cent hemoglobin (Sahli). The urine was negative. A preoperative diagnosis of intra-abdominal hemorrhage due to either a ruptured tubal pregnancy or "rupture of a vessel on a fibroid" was made. The patient was treated for shock and when she reacted a laparotomy was done. At operation the peritoneal cavity contained between two and three quarts of blood. The uterus was the seat of multiple fibroids, of which two were pedunculated and attached to the fundus. The larger one, measuring 10 cm. in diameter, had undergone complete torsion resulting in a ruptured varix on the posterior surface. A fundectomy including both fibroids was done. The patient received 200 c.c. of blood by autotransfusion and an additional 700 postoperatively. Her stay in the hospital was uneventful and she was discharged on the thirteenth day in good condition.

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7224 Fourth Avenue

BRAIN TUMOR COMPLICATING PREGNANCY*

BERNARD MANN, M.D., PHILADELPHIA, PA.

THE coincidence of brain tumor and pregnancy is rare. The literature reveals about 30 cases of this complication. According to Cushing, brain tumors, particularly gliomas, may either arise during pregnancy, or more likely their growth becomes accelerated during this state.

K. L., aged 24 years was admitted to the Mount Sinai Hospital on Sept. 23, 1932 because of severe headaches, dizziness, vomiting, and weakness of the left arm and left leg.

The last menstrual period was Feb. 17, 1932. The expected date of confinement was Nov. 24, 1932. During the first three months she vomited frequently, mostly in the mornings. She did not vomit during June and July, but in August the vomiting recurred.

Her past medical history was negative. She had two normal deliveries, two and four years ago, vomiting only the first two months with each.

The general physical examination on admission was as follows: The blood pressure was 114/75. The heart and lungs were normal. There was no edema. The uterus was enlarged to the size of a six months' pregnancy, fetal heart sounds were heard in the left lower quadrant.

The urine was negative except for a trace of albumin. Hb. 80 per cent; R.B.C. 4,270,000; W.B.C. 10,700; polymorphonuclears 75; small monocytes 24; large monocytes 1; total nitrogen, 26.4; urea nitrogen, 11.2; alkali reserve, CO_2, 45 volume per cent; blood sugar, 94; calcium, 9.6; chlorides, 572; Wassermann, Kolmer, and Kahn tests negative. Liver function test, bromosulphthalein, before dye injection, 0 per cent; fifteen minutes after injection 0 per cent; thirty minutes after injection, 0 per cent; sixty minutes after injection, 0 per cent. Icterus index, blood serum 3.

X-ray of skull and chest were negative. A lumbar puncture was done, the spinal fluid was under 8 mm. of mercury pressure, examination of the fluid was negative. She had a marked ataxia and slight weakness of the left arm and leg. There was a choked disc of two diopters of the left eye and one diopter, the right.

She was kept under observation and repeatedly examined to determine the location of the brain tumor.

The headaches, dizziness, and vomiting continued, becoming more severe. On October 14 she could not be aroused. It was then decided to terminate the pregnancy. A cesarean section was done under local anesthesia. She was delivered of a living female child, which died the next day. The day following the section she was not so stuporous, complained of headache but no vomiting. The next day the headache continued and the vomiting recurred, both sphenopalatine ganglia were cocainized, which gave her relief for a day, the above procedure was repeated with no relief.

The prompt improvement after evacuation of the uterus at the thirty-fifth week of pregnancy may have resulted from the decrease in blood volume and diuresis which occurred at this time.

Nov. 12, 1932, Dr. Francis C. Grant explored the posterior fossa by means of a suboccipital craniectomy and found the left cerebellar hemisphere to be larger than the right. Tap of this hemisphere revealed a deep seated tumor. Owing to the patient's condition the removal of the tumor was not attempted. She was discharged from the hospital December 7 in quite satisfactory condition, which continued until April, 1933 when the symptoms of vomiting and nausea, pain in left side of her head, cramp and pain in left arm and leg returned.

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She was reoperated upon May 25, 1933. A soft infiltrating tumor was found; four-fifths of which was removed from the left cerebellar hemisphere. *Diagnosis:* Medulloblastoma.

Three series of x-ray treatments were given, and the patient continued to live in fair condition, having bouts of vomiting and weakness until her death October, 1936.

The question that concerns the gynecologist is, shall pregnancy be terminated in cases complicated by brain tumor? The literature does not reveal an unanimity of opinion.

2019 PINE STREET

CERVICAL DYSTOCIA DUE TO SCARS FROM DEEP CAUTERIZATION

HARRY JAMES JORDAN, M.D., PITTSBURGH, PA.
(From the St. Francis Hospital)

PATIENT in this case had a deep cervical cauterization about nine months previous to the labor under discussion. This was not followed up by the usual dilatation of the cervix at the end of the six weeks' period. On July 17, 1938, at 10:30 P.M. I was called into consultation by the family physician at the patient's home.

Mrs. J. W., aged 33, gravida iii, para iii, all previous labors spontaneous and with no difficulty. She had been in good active labor for the past fifteen hours. Examination revealed a vertex presentation, L.O.A. position, presenting part engaged, no evidence of disproportion, fetal sounds L.L.Q., rate 120, external measurements within normal limits, membranes ruptured.

On rectal examination the presenting part was easily felt. There was no effacement and the external os would not admit the tip of the examining finger. At this time the contractions were of good quality, every three to four minutes. The family physician stated that this had been the case for the past fifteen hours. The patient was given ¼ gr. of morphine sulphate, and I remained with her until 7 A.M. the following morning. During this time the contractions remained the same and repeated rectal examinations revealed no further dilatation.

The patient was then advised to enter St. Francis Hospital at which time vaginal examination revealed a large, soft, bilaterally lacerated cervix, which would not admit the tip of the examining finger. The presenting part was fixed; could be felt in both fornices and the diagonal conjugate was ample.

One-fourth grain of morphine sulphate and 1/200 gr. of scopolamine were given on admission at 8 A.M. and at 4 P.M. of that afternoon. No change was noted in the caliber of the cervix, after a total labor of thirty-two hours.

Under gas ether anesthesia the operative area was prepared in the usual manner, following which each cervical lip was grasped with two pair of ring forceps. The anterior lip was incised as far as the bladder and the posterior lip as far as the rectum. The hand was then inserted completing the dilatation and delivery of a healthy male infant weighing 7 pounds 8 ounces by podalic version. The cervical incisions and old bilateral lacerations were approximated with No. 2 chromic catgut, after which the placenta was expressed. There was a very resistant fibrous ring at the level of the internal os which would admit two fingers and could probably be attributed to the scarification resulting from the earlier deep cauterization. Both the patient's and infant's stay in the hospital was uneventful and they were discharged on the twelfth day in good condition. The cervix was well healed and looked better than on admission.

AN INSTRUMENT FOR THE SAFE DRAINAGE OF OVARIAN CYSTS

ADRIAN W. VOEGELIN, M.D., F.A.C.S., PHILADELPHIA, PA.

BEFORE presenting a new technique for the removal of large ovarian cysts, I would like briefly to mention a few facts about the two common types which comprise most of the large cysts coming to operation.

Falling into fairly distinct pathologic classes are the pseudomucinous cysts and the probably equally frequent serous or papillary cystadenomas. Of these, the gynecologist will encounter several in the course of a year and may recognize them as often by inspection as by palpation.

The first, the pseudomucinous cysts, grow quite rapidly and in former days were often allowed to reach mammoth proportions (the 100 or 200 pound tumors of the literature). They tend to be unilateral, freely movable and pedunculated. Commonly multilocular, one of the locules usually is larger than the rest. They contain a gelatinous fluid which is not true mucin; while usually benign, they sometimes show papillary overgrowth and may become carcinomatous. According to Goodall "pseudomyxomatous ovarian tumors as a class are generally looked upon with suspicion owing to the frequency with which they pass over into the malignant state."

However, these cysts occasionally terminate fatally in another way, namely the production of the weird condition known as "pseudomyxoma peritonei" resulting from spilling of the contents into the peritoneal cavity either by spontaneous rupture or at operation. Cell implantation and multiplication take place with the production of masses of pseudomucin. Peritoneal irritation, adhesions, lymphatic blockage, and eventually death result. Spontaneous regression seldom happens.

The other type of large ovarian cyst is the serous or papillary cystadenoma. It is slower growing but may also reach a large size. It may be unilocular but if multilocular, has fewer chambers with one large one predominating. The other ovary is frequently affected. The characteristic serous contents, clear or blood tinged, and the papillomatous infoldings or surface growths distinguish this tumor. All of these papilliform tumors are definitely to be suspected, as they tend to carcinomatous change. Even if primarily benign they lie at the borderland of malignancy. Unfortunately, microscopic study may overlook the carcinomatous area so that Ghon's rule is of practical value; namely "Any papillary tumor showing growth into its wall or implants externally, is malignant until proved otherwise."

In general, malignancy is proportionately more frequent in ovarian tumors than in neoplasms of any other organ. Metastases from primary malignant new growths of the ovary occur in from 85 to 90 per cent of all cases. Implantation metastases occur through the cyst wall or from spilling of the cyst contents into the peritoneal cavity either by rupture or at the time of an operation. Metastasis also occurs by direct extension or by way of the lymph vessels and glands. Blood vessel extension is relatively rare in ovarian malignancy.

However, let us leave the subject of cyst pathology and consider that of surgical removal. Modern technique has made ovariotomy a comparatively safe procedure. As ovarian tumors grow older and more prone to malignancy, they usually increase in size. The larger the cyst coming to the operating table, the greater is the temptation on the part of the surgeon to drain it by trocar and cannula, and then remove the collapsed cyst through an ordinary short incision. If this is done, we know that there *always* occurs spillage of cyst contents from around the trocar puncture into the peritoneal cavity. If the cyst is wholly benign or is not infected, no harm may result. Since, however, carcinogenic cells or pseudomucin-secreting

*Presented at a meeting of the Obstetrical Society of Philadelphia, November 3, 1938.

goblet cells commonly multiply on the inside of an ovarian cyst rather than on the surface, this leaking of contained fluid from a nonbenign cyst is the commonest cause of metastatic recurrences. Occasionally if the transported cells are of low vitality they may atrophy or a chronic inflammatory process may enclose the implanted tissue and inhibit its growth. Otherwise the metastasis continues to spread until various peritoneal or other regions are involved, and disaster eventually follows. Because of this risk, pathologists and surgeons agree that whenever possible, ovarian cysts should be removed intact, through a sufficiently long incision even if it has to be extended to the costal margin. To make possible the safe use of a short incision, this instrument has been devised.* Its unique feature is the use of a ring of negative pressure to maintain a watertight junction between the smooth surface of the cyst and the flat surface of the attachment, which is less than two inches in diameter. A leak-proof channel carries a standard cannula and trocar size 22. While the apposed surfaces are hermatically sealed by means of the compressed rubber suction bulb, the trocar, with its cannula, is pushed into the largest cyst cavity. The point is than pulled up out of the way leaving the end of the

Fig. 1.

cannula protruding within the cyst cavity. By means of the usual suction pump, the fluid contents are aspirated through firm-walled rubber tubing into a large bottle. After a sufficient quantity has been removed, the collapsed sac with the apparatus still attached is then delivered outside the abdomen, ligated at its base and excised. If desired, the suction plate can be detached at any time after first applying firm clamps to the cyst wall from each side to keep in any remaining contents.

A possible advantage of this method is that there is no lifting of a large free mass out of the abdomen to cause a sudden relief of intra-abdominal pressure with consequent overfilling of blood vessels and the risk of cardiac embarrassment.

This method is not generally useful for (1) intraligamentary cysts or (2) cysts so adherent that they cannot be freely liberated. Good mobility is essential before applying the suction plate. It will fail occasionally when the cyst material is of such jellylike consistency that it will not flow through even the largest sized cannula, in which event the incision must be enlarged. Even in multilocular cysts of the more solid type, the emptying of one or more adjacent compartments by extending the trocar point through an intervening wall may produce an appreciable diminution in bulk and permit a shorter incision.

A recent operation at the Kensington Hospital for Women will illustrate the usefulness of this instrument:

Mrs. A. K., aged 52, noticed her abdominal enlargement for one year. Physical examination showed a large abdominal tumor hard and symmetrical and not freely movable because of its size. A midline incision, five inches long, revealed a right ovarian cyst about ten inches in diameter with smooth cyst wall and no evidence of

*Manufactured by the Penn Surgical Instrument Company, Philadelphia, Pa.

implants. One hundred cubic centimeters of clear fluid were free in the abdominal cavity. The cyst trocar was applied to its surface and nine quarts of brown rather thick material evacuated without any spillage. After reduction, the cyst was easily delivered and the pedicle clamped and severed. Incidental removal of a hard left ovary was done. Convalescence was uneventful. The pathological report was as follows: Right ovary: Papillary cystadenoma showing many areas of carcinomatous change. Left ovary: Papillary cystadenoma.

The patient received postoperative x-ray therapy for good measure.

1521 LINDLEY AVENUE

DISCUSSION

DR. GEORGE W. OUTERBRIDGE.—This apparatus is an exceedingly ingenious and, I believe, efficient simplification of an instrument that was in vogue in Germany some twenty years or more ago for accomplishing the same purpose. It consisted, as I remember, of two concentric metal tubes, the outer of which was connected with a suction apparatus and placed against the cyst wall, sucked a collar of this around the inner tube through which was thrust the hollow trocar connected with a second separate suction apparatus for evacuation of the cyst contents. This was, of course, somewhat cumbersome in arrangement, and so far as I know was never very widely used. The apparatus presented would seem to accomplish the same purpose in a much less complicated manner.

DR. VOEGELIN (closing).—I did not know that this principle of suction had been used before. At first we thought that we could use one suction apparatus to maintain both the systems but found it could not be done successfully. That is why the use of the rubber suction bulb is necessary.

AUTOMATIC TRANSUTERINE TUBAL INSUFFLATOR*

OSCAR H. BLOOM, M.D., BROOKLYN, N. Y.

TRANSUTERINE tubal insufflation as a diagnostic procedure has become almost universal since the epoch-making work of Rubin and Stein. For complete safety to the patient during this test, any mechanism used for insufflation must fulfill the following requirements: (1) Deliver a fixed quantity of gas per minute, (2) the total quantity of gas injected should be readily measured, and (3) the apparatus must be equipped with an accurate manometer to measure the intrauterine pressure of the gas.

Not all the types of apparatus employed have these safety devices and the literature reveals several fatal accidents, as reported by Moench,[1] Kern,[2] Mansfeld and Dudits,[3] and Weitzman.[4]

To insure the greater safety of the patient, I have devised an automatic insufflator that has proved itself to be fool-proof. This machine has been in use for the past eight months at the Gynecological Clinic of Dr. M. N. Hyams, at the New York Postgraduate Hospital, as well as in private practice. About 100 insufflations have been done and the mechanism has met every expectation.

This instrument consists of the following parts:

1. A motor driven air pump, which is so constructed that it delivers 60 c.c. of air per minute. This rate is unalterable and beyond the control of the operator.

2. An electrically controlled time clock (*X*) which can be set to run from one to fifteen minutes and which shuts off the pump at the end of the time predetermined by the operator. Thus if the operator wishes to inject 180 c.c. of air, the time clock is set at three minutes and one can be positive that no more than that quantity will be injected.

*Presented at a meeting of the Brooklyn Gynecological Society, October 7, 1938.

3. A mercury manometer (*Y*) wired with electrodes that automatically shut off the pump when the mercury rises to the pressure that the operator believes to be dangerous. The upper electrode (*U*) is adjustable, and it is set at the desired height of pressure before starting the insufflation.

4. A light indicator (*I*) that tells the operator when the pump is operating, or when it is shut off, either by the time clock or the pressure control.

5. An electrical switch (*S*) for the house current.

6. A starting button (*B*) to actuate the pump.

7. An outlet (*O*) for the air to the patient.

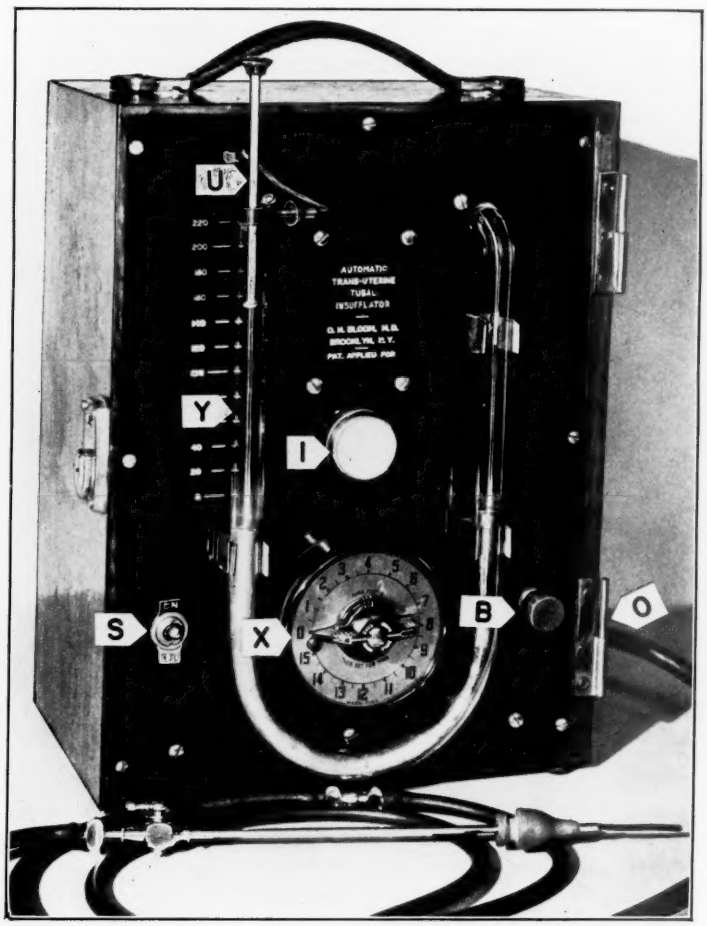

Fig. 1.

PROCEDURE

The patient is placed in a slight Trendelenberg position. The external genitals are scrubbed with tincture of green soap. The vagina and cervix are painted with mercurochrome. The cervix is grasped with a tenaculum and the Hyams' cannula is introduced into the cervical canal. Any nonirritating antiseptic solution may be introduced into the vagina to act as an indicator of air leakage from the external os.

The line switch (*S*) is thrown *ON*. The adjustable electrode (*U*) is set for any safe pressure, usually 140 mm. of mercury. The time clock (*X*) is set for three minutes in order to inject 180 c.c. of air, and the actuating button (*B*) is pressed.

The light indicator begins to glow and the operator knows that the air pump has begun to run. As the air begins to flow into the uterus, its pressure rises, as shown by the rise in the column of mercury in the manometer. If the tubes are patent, the apparatus will run for the allotted time (three minutes in this case) and then shut itself off, by means of the automatic time clock, thus insuring the injection of the quantity of air desired. However, in cases of complete stenosis, the mercury will continue to rise until it will make contact with the adjustable electrode (*U*), set at the safe pressure of 140 mm., and the pump will be shut off instantaneously, thus not allowing any more air to be forced into an already distended genital tract.

This automatic type of insufflator, which has been tried out in about 100 cases, will control: (1) The rate of flow of the air, (2) the total quantity of gas injected, and (3) the maximum pressure desired of the intrauterine gas.

REFERENCES

(1) *Moench, G. L.:* J. A. M. A. **89:** 522, 1927. (2) *Kern, R. A.:* J. A. M. A. **86:** 623, 1926. (3) *Mansfeld, O. P., and Dudits, A.:* Zentralbl. f. Gynäk. **58:** 2117, 1934. (4) *Weitzman, C., and Cohen, M.:* New York State Med. J. **37:** 1582, 1937.

Held, E.: A Clinical Study of Adnexal Tuberculosis, Gynéc. et obst. **35:** 327, 1937.

The writer presents an analysis of 30 cases of adnexal tuberculosis observed during a five-year period and confirmed microscopically and bacteriologically, with an evaluation of the diagnostic methods employed. The fact is stressed that so frequently the diagnosis is only made at operation because the condition, though not uncommon, is not suspected.

Eleven patients had pleurisy preceding the pelvic condition by several years. Pleurisy and extrapulmonary tuberculosis are important in the history. Coincident or previous pulmonary tuberculosis was not common. In only three instances did tuberculous peritonitis of infancy precede the pelvic lesion. Contrary to Jayle's contention, there is no apparent tendency for gonorrhea and pelvic tuberculosis to coexist.

Sterility in the absence of a history of gonorrhea or postabortal infection should suggest the possibility of pelvic tuberculosis.

Little diagnostic value is attached to the blood picture and special tests such as Besredka's and Vernes'. Blood sedimentation is more rapid in tuberculous adnexitis than in the pyogenic variety and this acceleration is not uncommon in the complete absence of fever. Nevertheless, it is of no value in differential diagnosis. Salpingo-oophoritis of tuberculous origin responds in a very variable manner to pelvic diathermy. Poor response to this method of treatment cannot be considered as suggestive of tuberculosis.

Cul-de-sac puncture with guinea pig inoculation is advocated as a most useful procedure in the diagnosis of adnexal tuberculosis, even where mixed infection is present. This may be repeated several times and obviate the need for colpotomy which when done in the presence of tuberculosis sometimes results in fistulization.

Exploratory laparotomy is indicated when the diagnosis is not clear. It was performed by the author in six instances of his series.

ARNOLD GOLDBERGER

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

STUDY OF MATERNAL DEATHS IN CHICAGO

FRED L. ADAIR, M.D., AUGUSTA WEBSTER, M.D., AND LUELLA NADELHOFFER, M.D., CHICAGO, ILL.

THE Maternal Welfare Committee of the Chicago Gynecological Society studied maternal deaths in Chicago during 1934, 1935, and 1936. Each hospital delivering maternity cases was invited to have membership on this committee. Data were obtained by questionnaire and sent to the representative of the hospital in which the death occurred.

In 1936, the Board of Health cooperated in this study by supplying an obstetrician to investigate all maternal deaths by examination of the records and by interviews with the physicians in charge of the cases where possible. This material was then carefully studied by the Maternal Welfare Committee, and it was found that a large percentage of deaths appeared to have preventable factors.

It was therefore decided to invite interested societies to cooperate in plans to reduce maternal and infant mortality and morbidity.

The following organizations were represented: American College of Surgeons, Chicago Hospital Council and its administrative section, Chicago Medical Society, Infant Welfare Society, Catholic hospitals of the Archdiocese of Chicago, Chicago Pediatric Society, Chicago Gynecological Society, and the Chicago Board of Health.

As a result of this meeting a permanent committee was organized and named "The Joint Maternal Welfare Committee of Cook County." Dr. Fred L. Adair was chairman and Dr. E. L. Cornell secretary of this committee. Each organization was represented by two members.

Policies and procedures were formulated which were believed to be the minimum requirements essential in the conduct of a well-organized maternity division. These were in accordance with the highest scientific standards, but at the same time were practical enough to be easily applied in the average hospital.

The Chicago Board of Health, Herman N. Bundesen, President, then adopted "Regulations for the Conduct of Maternity Hospitals, Maternity Division of General Hospitals and Nurseries for the Newborn."

The regulations provided for complete physical separation of the maternity unit from the remainder of the hospital and for isolation facilities for the infected patient. They also required a well-equipped nursery for the care of the normal newborn, an isolation nursery, and a formula room. Special provisions were made for the care of premature and immature infants.

Minimum equipment for the maternity division was outlined including the essentials for the labor, delivery rooms, and nurseries.

Maternity hospitals were required to maintain personnel consisting of attending physicians, nurses and others adequate in training and numbers to carry on the proper routine and meet emergencies arising in such institutions. The work of the obstetric department was to be under the control of the obstetric staff—one of the members of which was to act as chairman of the department of obstetrics. He was to be a qualified specialist in obstetrics or obstetrics and gynecology. Each hospital was required to provide a competent obstetric staff for consultation and to control the obstetric procedures in the hospital.

Suggestions were made to the hospitals for the professional qualifications of the obstetric staff. Complete and detailed case records were required in all cases, including ante-partum and detailed hospital records.

Visitors in the maternity division were limited to two a day exclusive of the husband. Infants at no time were to come in contact with any visitors, and children under 16 years of age were excluded.

All operative procedures and medications were to follow generally accepted indications. The delivery rooms were to be conducted in strict accordance with surgical technique. The procedure of the personnel followed the concept that one who comes in contact with any patient should carry out aseptic technique before coming in contact with another patient. This precaution is especially important in connection with the care of parturient and puerperal women and newborn infants.

The majority of Chicago hospitals were cooperative and many willingly made many changes in their physical set-up and personnel in order to comply with these regulations.

It was evident, however, that in order to assure continued compliance periodic inspections would be necessary.

The Chicago Board of Health maintains a staff of physicians and nurses for this work. Monthly inspections are made, problems are discussed, and a written report is made in duplicate to the Board of Health and to the hospital administration.

Any difficulties or differences in interpretation or application of the regulations are referred to the Joint Maternal Welfare Committee of Cook County which acts in an advisory capacity to the Board of Health of the City of Chicago and as a liaison committee between doctors, hospitals, and the Board of Health.

INFORMATION CONCERNING NEW STANDARD CERTIFICATE OF LIVE BIRTHS AND NEW STANDARD CERTIFICATE OF STILLBIRTHS

THE American Committee on Maternal Welfare has pointed out the great need for additional medical information with respect to all births (live and still). For the reduction of mortality connected with birth, accurate information must be available with respect to prenatal and natal conditions. This information is necessary not only for the reduction of fetal and infant death rates, but also for the reduction of the maternal death rate and for the improvement of maternal and child health.

The committee has called attention to the magnitude of the loss of life connected with pregnancy and childbirth. The total loss from these causes in 1935, as shown by the Bureau of Census figures, was 161,249 lives, including 14,296 maternal deaths (12,544 deaths assigned to pregnancy and childbirth, and 1,752 deaths in which pregnancy or childbirth was a complicating factor), 77,119 stillbirths, and 69,834 infant deaths in the first month of life, of which 56,262 were due to prenatal and natal conditions.

Official State health agencies are urged to adopt the new standard stillbirth and birth certificates including supplementary data.

Uniform reporting of stillbirths throughout the United States can only be made possible when every State has adopted a standard certificate of stillbirth and has accepted the American Public Health Association definition of stillbirth, i.e., a stillborn child is one which shows a complete absence of life, no breathing, no action of heart, no movement of voluntary muscles.

The supplementary data for all live birth certificates referred to above is as shown in Chart 1.

Chart 1.

Suggestions by Children's Bureau for optional items to be carried at the bottom of the Birth Certificate.

Supplementary data below are not a part of the legal certificate.

29a. *Pregnancy*, Complications of: _____

_____

b. *Labor*, Complications of: _____

_____ Induced? _____

c. Was there an operation for delivery? _____ yes or no

State all operations _____

d. Did baby have any: _____

(1) Congenital malformation? _____

Describe: _____

(2) Birth injury? _____ Describe: _____

e. Was a prophylactic drug used in the baby's eyes? _____ If "yes" state drug _____ yes or no

As no standard certificate of stillbirth has ever been issued by the Bureau of Census prior to this year, and as only seven States have a stillbirth certificate at the present time, the portion of the standard stillbirth certificate giving information in addition to that received from all births is printed in Chart 2.

Chart 2.

Certificate of Attending Physician or Midwife

25. Did child die before labor? _____

during labor? _____

26. *Pregnancy*, complications of: _____

27. *Labor* (a) Complications of: _____

_____ (b) Induced? _____

28a. Was there an operation for delivery? _____

_____ yes or no

b. State all operations, if any _____

_____

c. Did child die before operation? _____

or during operation? _____

29. Cause of stillbirth (State only morbid conditions causing fetal death. Do not use such terms as prematurity, asphyxia, etc.)

a. Fetal causes: _____

_____

b. Maternal causes: _____

_____

30. I hereby certify, that I attended the birth of this child, who was born dead at the hour of _____ M. on the date above stated.

Signature _____ Title _____

Address _____

_____

31a. Burial, cremation, or removal _____

31b. Place _____ 32c. Date: _____ Month day year

32a. Signature of person burying the body _____

32b. Address _____

33a. Statement of local registrar or coroner if physician was not present at stillbirth. _____

_____

33b. Signature _____ Title _____

34. Registrar's own signature _____

35. Date filed with local registrar _____

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 6, 1938

The following papers and case reports were presented:

Management of an Institutional Outbreak of Infectious Diarrhea of the Newborn Infant. Drs. R. L. Roddy, J. S. Forrester and H. Landow. (By invitation.) (For original article, see page 1037.)

X-Ray Localization of the Placenta by Soft Tissue Technique and Without the Use of Opaque Media. Dr. R. Manges Smith. (By invitation.)

Implantation of Ovary in the Uterine Cornu. Dr. Margaret C. Sturgis. (For original article, see page 1048.)

MEETING OF NOVEMBER 3, 1938

The following papers were presented:

An Instrument for the Safe Drainage of Ovarian Cysts. Dr. Adrian W. Voegelin. (For original article, see page 1053.)

Syphilis in Relation to Gynecology and Obstetrics, With Special Reference to Diagnosis and Treatment. Dr. John A. Kolmer. (By invitation.)

Arsenical Treatment Reactions Among Syphilitic Pregnant Women, With a Report of Seven Maternal Deaths From Syphilis Therapy. Dr. Norman R. Ingraham. (By invitation.)

MEETING OF DECEMBER 1, 1938

The following case report and papers were presented:

Brain Tumor Complicating Pregnancy. Dr. Bernard Mann. (For original article, see page 1051.)

The Effect of the Female Hormones and of Pregnancy Upon the Ureters of Lower Animals as Demonstrated by Intravenous Urography. Drs. Franklin L. Payne and Philip J. Hodes. (For original article, see page 1024.)

The Therapeutic Value of Low-Dosage Irradiation of the Pituitary Gland and Ovaries in Functional Menstrual Disorders and Sterility. Drs. Charles Mazer and George Baer. (For original article, see page 1015.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 21, 1938

The following papers were presented in a symposium on Rare Ovarian Tumors:

1. **More Recent Developments in Ovarian Tumors.** Dr. Walter Schiller (by invitation).

2. **Arrhenoblastomas.** Dr. A. E. Kanter. (Published elsewhere.)

3. **So-Called Lutein Cell Tumors.** Dr. Otto Saphir (by invitation). (For original article, see page 1008.)

4. **Variations of Lipoid Content in Certain Ovarian Tumors.** Drs. R. B. Greenblatt, J. P. Greenhill, and W. R. Brown. (For original article, see page 929.)

MEETING OF NOVEMBER 18, 1938

The following paper was presented by invitation:

Hormone Factors in the Toxemias of Pregnancy. Dr. Howard C. Taylor, Jr. (For original article, see page 963.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 4, 1938

The following paper was presented:

Fetal and Neonatal Disease and Death. Dr. Fred L. Adair and Edith L. Potter, Chicago, Ill. (By invitation.) (For original article, see page 993.)

MEETING OF OCTOBER 7, 1938

The following papers were presented:

Automatic Transuterine Tubal Insufflation. Dr. Oscar H. Bloom. (For original article, see page 1055.)

Primary Ovarian Pregnancy. Dr. Harris M. Rabinowitz.

A Ten-Year Study of Ectopic Gestation at Beth-El Hospital. Drs. Nathan Reibstein, Samuel Weiner and Harris M. Rabinowitz.

The Interposition Operation. Drs. Oscar M. Bloom, Abr. Heinrich and Abr. Koplowitz.

Ruptured Interstitial Pregnancy in the Fourth Month. Dr. Philip Oginz.

A Modified Sturmdorf Operation for Vesicovaginal Fistula. Dr. Abraham Koplowitz. (For original article, see page 1045.)

Ten Years of Obstetrics at the Beth-El Hospital. Drs. Wm. Levine, Harry Warwick, H. Warwick and P. Oginz.

MEETING OF NOVEMBER 4, 1938

The following papers and case reports were presented:

Diabetes in Pregnancy. Dr. Martin M. Shir. (For original article, see page 1032.)

Pelvic Examination in Suspected Placenta Previa. Dr. Stanley C. Hall.

The Criteria and Significance of Engagement. Dr. Arthur S. MacGregor.

What Is a Test of Labor? Dr. Frank P. Light.

The Postmature Fetus. Dr. John Casagrande. (For original article, see page 1028.)

"Once a Cesarean, Always a Cesarean." Dr. G. R. MacLachlan.

MEETING OF DECEMBER 2, 1938

Massive Intraperitoneal Hemorrhage Resulting From Rupture of a Superficial Vein of a Uterine Fibromyoma. Dr. Anthony L. Shelfo. (For original article, see page 1049.)

Granuloma Inguinale (Venereum). Drs. Samuel A. Wolfe and Eugene J. Tortora.

The Etiology and Treatment of Endocervicitis and Cervical Erosion. Dr. Anthony Wollner. (For original article, see page 947.)

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Analgesia and Anesthesia in Labor

Minnitt, R. J.: Analgesia in Midwifery, Brit. M. J. 2: 538, 1937.

The author outlines the present methods for obtaining analgesia in labor. Two main types are available: (1) drugs given orally or hypodermically, and (2) inhalation analgesia.

The apparatus and technique are described whereby the patient feeds herself a gas and air mixture (nitrous oxide) with each pain during the first and second stages of labor.

Maternity nurses receive special training along these lines of procedure, and specially trained candidates in gas analgesia receive certificates to that effect.

Gas and air analgesia is contraindicated in abnormal cases, i.e., cardiacs, phthisis, bronchitis, albuminuria, and hypertension.

The demands of the parturient for the best relief of labor pains are gaining wider recognition and drug therapy is giving place to gas analgesia.

F. L. ADAIR AND S. A. PEARL.

Bonar, Barnet E., and Blumenfeld, Charles M.: Obstetric Anesthesia, Surg. Gynec. Obst. **66**: 179, 1938.

There is need for greater use of precise methods to determine the effect of anesthetics and analgesics on uterine contractions and on the fetus. As far as the uterus is concerned hysterography is the method of choice at present. Especially is this true of external hysterography since it is reasonably accurate, simpler, safer for the patient, and less subject to criticism. A procedure recently described by Rosenfeld and Snyder offers great possibilities in studying the effects of anesthetics and analgesics upon the fetus. Experiences with this method are related and the observations of Rosenfeld and Snyder regarding the existence of apparently physiologic intrauterine fetal respiratory movements which are depressed or stopped by some of the anesthetics and analgesics are confirmed. There is evidence that this method may be of value in studying the effects of these agents upon uterine contractions also. Direct and color motion picture observations upon animals anesthetized by cord transection are reported and the advantages and disadvantages of the method are discussed. In order to obtain more accurate data there is need for an instrument which will record these movements graphically. It is possible that this may be accomplished in the near future by using an instrument recently devised by Fenning to record graphically small changes of volume. Further studies along these lines are being pursued.

WILLIAM C. HENSKE.

Wolf, Willi: The Cause of Pain in Labor and Its Significance for Conduct of Delivery, München. med. Wchnschr. **85**: 824, 1938.

Wolf discusses labor pains and their probable causation. From clinical observation he has come to the conclusion that real pain in active labor is caused by the dilatation of the internal os and of the external os, and that because of this it is easier to explain all painful and painless processes in pregnancy, labor, and the puerperium than by the theory that the pain is due to uterine contractions. Furthermore he feels that this new theory has possibilities which are of some importance also for the management of labor and delivery.

C. E. PROSHEK.

Paton, M. Donald: A Study of a Few Common Types of Obstetric Analgesia, Texas State J. Med. **33**: 506, 1937.

In the experience of Donald M. Paton (Houston) morphine-scopolamine, scopolamine-sodium amytal, and nembutal-scopolamine, when properly used, give satisfactory amnesia in 80 per cent of cases. These drugs do not increase the incidence of operative delivery, and danger to the baby is negligible in the hands of one trained in the use of these analgesics. Nembutal seems to be safer than twilight sleep or sodium amytal with scopolamine. Twilight sleep used in a toxic patient may provide a definite threat to the life of the baby. Nembutal can be started a little earlier in labor than twilight sleep or scopolamine-sodium amytal and is therefore perhaps preferable to them in multiparas.

J. P. GREENHILL.

Bell, Warren W.: Experiences With Scopolamine in Obstetrical Practice. Reasons for Its Discontinuance by the Author, West. J. Surg. **46**: 276, 1938.

The writer analyzes his experience with 441 patients within a period of between two and a half and three years. Of the total number 225 had been given scopolamine and 216 nembutal. He found that scopolamine usually is effective in producing a desirable degree of amnesia and analgesia, but that its cumulative effect upon the respiratory center of the infant so often results in asphyxia that he has not felt justified in continuing its use. Although dangers of scopolamine to the life of the mother may usually be eliminated, Bell is convinced that neither the mother nor he, as practitioner, can justify its use merely in an endeavor to minimize the suffering of the mother in childbirth.

The experience with 216 patients to whom nembutal was given has convinced the author that the barbiturates are not only as effective as scopolamine, but that they are far safer for both mother and child.

J. P. GREENHILL.

MacPhail, Gray, and Bourne: Pentothal Sodium as a Hypnotic in Obstetrics, Canad. M. A. J. **37**: 471, 1937.

They gave pentothal sodium to 238 women in labor without any noticeable harmful effects to either mother or child. It appeared that, unlike ordinary barbiturates, this thio-derivative did not cause excitement at any time. Furthermore, the hypnotic action of pentothal sodium appeared to be attended by a marked degree of amnesia. One of the conclusions reached was that labor was shortened in duration. The method of administration was to give capsules by mouth, 4 gr. being allowed as soon as pains were definitely established, 3 gr. being repeated half an hour later, and again at the end of one hour. If required, 2 to 3 gr. might be repeated every half hour to one hour if the effects seemed to be wearing off.

Scopolamine, 1/100 to 1/150 gr., was given at the time of the first dose. Pentothal sodium may also be given in solution per rectum. The dose used was 7½ gr. dissolved in 25 c.c. of water and repeated in an hour's time. A further series of 120 obstetric cases were treated in this manner and the results were quite satisfactory.

J. P. GREENHILL.

Siegler and Beris: Evipal Soluble Rectally Applied in Obstetrics. A Preliminary Report, New York State J. M. **38**: 1071, 1938.

Evipal soluble was used. Supplied in ampules of 3 gm. This amount was dissolved in 90 c.c. of distilled water and applied rectally. To women weighing less than 150 pounds 30 c.c. (1 gm.) of solution was administered, to women weighing over 150 pounds a larger dose of 45 c.c. (1.5 gm.).

The authors believe that evipal soluble is a safe analgesic and amnesic to be used rectally in obstetrics. There are no deleterious effects on either the par-

turient mother or the infant. The method of administration is simple and no special nursing care is necessary. Repeated doses may and should be used when necessary.

J. P. GREENHILL.

Emmert and Goldschmidt: Obstetrical Analgesia With a New Barbiturate, South. M. J. **31:** 240, 1938.

In 200 consecutive deliveries conducted under analgesia secured with sigmodal no maternal or fetal deaths occurred. The duration of labor was definitely shortened and no deleterious effect upon mothers or babies was noted. The operative frequency was decreased. Remarkable restlessness was noted in only 8 cases, and post-partum hemorrhages occurred in 4 cases. Resuscitation was required in 4 cases due to anomalies or position of the cord.

The authors believe that sigmodal can be administered without risk to mother or child. It results in complete amnesia and analgesia in nearly 80 per cent of the cases.

J. P. GREENHILL.

Abrams, Samuel F.: Block of Pudendal Nerve in Obstetrics, J. Missouri M. A. **35:** 81, 1938.

The technique of injection is as follows: With the patient in the lithotomy position, the inner margin of the tuberosity of the ischium is located. Usually a point on a line with the anus, but 2 cm. medial to the tuberosity, is the best site of injection. The tip of the needle is inserted and directed outward to the surface of the tuberosity where about 10 c.c. of a 0.5 per cent novocaine solution is injected. The needle is in constant motion to avoid intravenous injection. The needle is then withdrawn about halfway and redirected toward the spine of the ischium, which is easily palpated with a finger in the vagina. Here another 10 c.c. is injected. Aspiration must be tried before injection to be certain that the needle is not in a blood vessel. The same procedure is then followed on the opposite side. In a period varying from one to five minutes it will be found that the lower third of the levator muscles and the perineal muscles have relaxed so markedly that the fist can be placed in the vagina. The needle found most satisfactory has been a 21 gauge needle about 3 inches long and with a guard at the shank of the needle to obviate loss of the needle in case of breakage.

A series of 400 cases of pudendal nerve block is reported by the author. No obstetric complications such as post-partum hemorrhage should arise as the anesthetic does not involve the uterine musculature. No cases of shock were encountered because care was taken not to inject novocaine intravenously.

As the skin of the perineum is to a minor extent supplied by other nerves, complete local anesthesia is not obtained. If this is desired, infiltration is necessary. The only contraindication is infection about the site of the proposed injection.

J. P. GREENHILL.

Woodbury, Hamilton and Torpin: The Relationship Between Abdominal, Uterine and Arterial Pressures During Labor, Am. J. Physiol. **121:** 640, 1938.

By means of a set of differential manometers simultaneous records were taken during normal labor pains of (1) the systemic arterial pressure; (2) the effective maximum of maternal blood pressure to the placenta; (3) the total intrauterine pressure; (4) the contribution of the uterine wall to the intrauterine pressure.

It was found that in the woman in labor uterine contractions result in smooth symmetrical pressure rises which vary in height from 25 to 95 mm. Hg and subject the uterine wall to an average maximal tension of 500 gm. per square centimeter of uterine wall cross area. During delivery of the head, the average maximal expulsive force was 15 kg. The frequency and duration of uterine contractions

were unaffected by morphine, nitrous oxide-oxygen, the barbiturates, cyclopropane, ether and chloroform. The strength of the uterine contractions, markedly reduced by ether and chloroform, was unaffected by the other anesthetics. All of the above drugs reduced the contribution of the abdominal muscles to the intrauterine pressure.

During labor pains the systemic blood pressure increases and the pulse pressure widens. The effective maternal arterial pressure to the placenta diminishes—sometimes to zero. The pressure which irrigates the placenta is increased by obstetric anesthetics and by epinephrine.

J. P. GREENHILL.

Cameron, G. R.: Some Recent Work on Barbiturates, Proc. Royal Soc. Med. **32**: 309, 1939.

Toxic effects are sometimes seen after administration of quite small amounts of barbiturates. This is a matter of almost universal experience. The quick acting members of the group, nembutal and evipan sodium, are more frequently concerted than the slow acting forms, such as barbital sodium and phenobarbital sodium. The liver is not infrequently and permanently damaged by prolonged administration of nembutal. There is a feeling among clinicians and pathologists that it is not wise to give barbiturates, even in small doses, to subjects with liver disease.

HUGO EHRENFEST.

Casalta, E.: Accident from Spinal Anesthesia in a Low Cesarean Section, Bull. Soc. d'obst. et de gynéc. **27**: 437, 1938.

The author reports a sudden death from spinal anesthesia which occurred while the uterine incision was being closed at the time of a low cesarean section. This is the first accident of the kind encountered by the author. He mentions other similar deaths reported by Cotte and Bansillon, and by Brochier and Ambre.

J. P. GREENHILL.

Cambon: Low Cesarean Section and General Anesthesia. Preventive Procedure for Control of Bleeding, Bull. Soc. d'obst. et de gynéc. **27**: 440, 1938.

Cambon has given up the use of spinal anesthesia for cervical cesarean sections, because he encountered a sudden death due to it, because his colleague, Plasse, also had a similar accident and because he knows of a few other sudden deaths from spinal anesthesia which have not been published. Hence Cambon believes that spinal anesthesia is more dangerous than ether and he now uses ether. For the control of bleeding he injects pituitary extract directly into the uterine muscle and also ergotamin subcutaneously.

J. P. GREENHILL.

Correspondence

Rural Obstetric Practice a Generation Ago

The following letter was received recently from Dr. Ferdinand J. Smith, of Milford, Iowa, in response to a general appeal to the physicians of the State for assistance in compiling data on home deliveries. It occurred to the recipient that Dr. Smith's letter was of too much historic value to justify its burial in a filing cabinet, and consequently permission was sought to publish it after a few minor alterations. This request was graciously granted, and the Editor of the JOURNAL offered his cooperation.

E. D. PLASS.

Milford, Iowa
April 29, 1938.

My dear Doctor Plass:

I have recently received your letter and the enclosed questionnaire, but cannot be of assistance to you since I am no longer in practice, although I have records of over four thousand confinement cases attended during my professional life. There are, however, certain data which I can give you from memory in the hope that they may be worth while.

I was graduated from the Medical Department of the State University of Iowa on March 2, 1887, after three courses of lectures of four months each. My undergraduate, practical experience in the office of Dr. W. F. Peck, then Chief Surgeon of the Rock Island Railroad and Dean of the Medical Department at Iowa City, was limited to surgery. I did not see the ordinary diseases of childhood, lung fever, typhoid fever or, in fact, any other internal medical cases until I began to practice medicine. The only obstetrics I saw was what the Professor of Obstetrics, Dr. J. C. Schrader, demonstrated on a manikin, which was, I suppose, better than nothing.

The majority of my obstetric deliveries occurred between the time of my graduation and January, 1904, when I was appointed full-time Professor of Chemistry and Dean of the Junior College of Medicine at Drake University, Des Moines. I remained in these positions for several years, but during the vacation periods had a small obstetric practice near Lake Okoboji where I spent the summers. In June, 1913, I resumed the practice of medicine and until 1919 was very active, especially in obstetrics. During this period, there were two days, on each of which I attended five confinements. From 1919 I lived at my home on Lake Okoboji and for some years did considerable practice, but gradually began to taper off and am now retired.

I still remember my first obstetric case. I arrived at the patient's home, examined her but failed to locate anything, and then began to get excited, since I did not seem to get anywhere. Finally I decided it was foolish to worry. Why worry? The mares, the cows, the ewes, all the farm animals had their offspring without assistance and got along fine. In good time, I was able to locate the presenting part and to determine the position and was gratified to find it normal. By continuing to exercise masterly inactivity, the baby eventually arrived, as big as life and twice as natural. After severing the cord, I watched the old neighbor lady wash and dress the baby, and assisted her in dressing the cord. I was beginning to think about going home when she suggested to me that it might be a good time to remove the afterbirth. I was very glad that she spoke of it but did not tell her so, because I had forgotten all about it. On examination I found the placenta in the vagina and removed it easily. After this experience, I went to my

obstetric cases with a feeling of confidence, convinced that the main thing to do was to give nature a chance. This may be the reason why I never lost a mother.

The mothers' ages ranged from 13 to 52 years. The average number of children to each mother was about a dozen; there were few with less than six, and in two families I attended the twenty-first and twenty-second confinements, respectively. There were very few stillborn children.

Of course, I had experience with all the normal fetal positions as well as with many abnormal, or undeliverable, presentations, in which it was necessary to use the appropriate operative procedures. There were quite a number of shoulder presentations, which I delivered by turning, usually under ether, but in quite a few cases without any anesthesia. One patient had twelve breech presentations, one shoulder presentation, which I turned, and one normal cephalic presentation. I can recall two face presentations. The first, with the chin forward and to the right, gave no trouble other than a prolonged period of delivery. In the second case, the chin was to the left and posterior. The patient was 32 years old, and this was her first baby. I was called by telegraph at nine in the evening, and reached the home, 25 miles distant, by daylight the next morning (horse and buggy days). The bag of waters had ruptured, and most of the fluid had escaped, but there was no dilatation and with each pain there was a further loss of fluid. By that evening, the patient was becoming impatient, and I suggested consultation. It was not until 11:00 P.M. that the consultant arrived. He thought it would be best to turn, but I told him that there was practically no water left in the uterus and that it would be impossible to turn under such circumstances. Nevertheless, he insisted upon trying and, with the consent of the patient, made the attempt, but found that he could not even introduce his hand into the uterus—there was too little dilatation. Then he wanted to introduce forceps and deliver instrumentally, and the husband asked him to try. I demurred and told him it would be dangerous, but in spite of this he went ahead. Naturally, he failed even to introduce the blades, and then gave it up for a bad job and went home. By morning I was able to diagnose a chin posterior, which is ordinarily not deliverable. The only other procedure, except to give nature more chance, was craniotomy, which was refused. Exactly at noon, the head adjusted itself so that the chin was in the anterior position, and in a short time the baby was born. The child was dead, but the mother made a good recovery and the next time had twins. I forgot to say that this first baby weighed 12 pounds at birth.

All of these deliveries were conducted in town or farm homes. In those days, physicians did not look upon childbirth as a disease, but rather as a physiologic process which should be treated accordingly, unless there were complicating conditions. The water supply was usually from surface wells, rarely from cisterns, and light was obtained from a candle or kerosene lamp. A doctor was expected to be able to pass a catheter without exposing the patient. I can still do it. There were no indoor bathrooms, and the toilets were the old-fashioned privy vaults. Instead of toilet paper, it was quite customary to use corn cobs. In the whole of Sioux County, I knew of but one bathroom.

The great bulk of the people were then able to pay the standard obstetric fee, which was $5.00 in town and $10.00 in the country, regardless of time or distance. The longest trip I made to attend a confinement was from Alton, in Sioux County, to Alvord, in Lyon County, a distance of fully fifty miles.

If I were to practice obstetrics now, I would refuse to attend a patient anywhere else than in the home. Patients become immune to any bacterial organisms in their own homes, whereas, even in the best regulated hospitals there are of necessity a great variety of organisms from many sources.

There was no prenatal care. Sometimes the husband or, more rarely, the wife would drop in at the office to advise me about the date of the coming event and to urge me to come quickly when I received a call. Patients did not report for examination or bring urine specimens for testing. It was only when edema complicated the pregnancy that we called for some urine and examined it for albumin and casts. Blood pressure appliances were not yet in use, and bacteriology was still in its infancy.

In my first cases of puerperal eclampsia (six months after I began practice), I used large doses of morphine hypodermically, to reduce the convulsions, and hot packs. The baby was born prematurely and eclampsia did not develop until four hours after delivery. The patient made a good recovery. All of my other puerperal convulsive patients were treated with Norwood's tincture of Veratrum viride, 15 minims hypodermically, repeated every thirty minutes until the pulse rate was 55 to 65 per minute. At the same time the patient was wrapped in a cotton flannel blanket wrung out of hot water, and ear corn, taken out of boiling water, was placed down both sides of the patient's body outside the blanket and under the quilt. This was continued until the edema was very much lessened and, in some cases, this result was achieved in no more than thirty minutes. It was rare that there were any more convulsions after such treatment. I had 18 or 20 eclamptic cases in my own practice and in consultation with other physicians, and did not lose a single mother. If treatment was begun early enough, the child also usually survived. (A paper on this subject was presented before the Northwestern Iowa Medical Society, April 30, 1919, and was published in the *Journal of the Iowa State Medical Society*, in August, 1919.)

The great bulk of my deliveries were spontaneous: among more than 4,000 cases, there were not over 30 instrumental deliveries. Once, I used the instruments on an aftercoming head, for fear that the baby might be asphyxiated. When I did use forceps, I produced traction with only two fingers, having found that this maneuver gave the patient much relief from pain by relieving the uterus of part of its muscular labor. I never gave anything to increase the activity of the uterus before delivery, except in certain cases where my experience indicated the liability of a relaxed uterus with consequent hemorrhage. In these instances, I gave a capsule containing 10 gr. of quinine sulfate immediately before birth. If this had not been done and hemorrhage appeared, I applied cloths wrung out of freshly drawn well water over the lower abdomen, and gave a teaspoonful of fluid extract of ergot. Perineal wounds were repaired immediately with catgut sutures. A wash boiler half full of boiling water served to sterilize dishes, old muslin and towels and also provided a supply of sterile water. There were no rubber gloves available, but I washed my hands thoroughly with soap and hot water, used a nail brush carefully, and sometimes immersed my hands in a solution of permanganate of potash. The vulva was not shaved.

Vaginal examinations were made only when indicated to follow the course of labor or to explain the cause for delay. Examinations per rectum had not yet been introduced. If an anesthetic was used, it was not given until the head engaged the perineum and was employed then only to safeguard the perineum. Ether was the usual anesthetic and was generally administered by one of the old ladies, or, perhaps, by the husband. On one occasion, I had the hired man give the ether, because the husband would not do it and no old ladies happened to be available. Unless there was a bronchial condition contraindicating its employment, I always felt safe in using ether. When there was evidence of bronchial involvement, I would either dispense with an anesthetic entirely or would give chloroform myself. Many labors, even those with the first child, were terminated within eight hours, particularly in women having a lanky build, whereas plump women usually had a harder time of it in their first labors. Faulty, even though not abnormal, positions led to more severe first labors than if the fetus were in a more normal position. As a rule, the second child came more easily, the third one much more so, and after that it was nip and tuck between the stork and myself. My patients were almost entirely of German and Dutch extraction. I was much impressed by the fact that most of the mothers were comparatively youthful looking. In certain large family groups it was difficult to pick out the parents from the older children.

In those days there were no trained nurses, but the older women, who had arrived at the end of their childbearing, would help out their younger neighbors. And they acquitted themselves well. *They did as they were told without question.*

Every one of my living babies was blessed with a living mother. And I was not the only doctor who had such an experience. It is my personal conviction that there is altogether too much meddlesome midwifery on the part of physicians, and that

there is too much chance for infection in hospitals. Perhaps the fact that too many of the mothers or (and) fathers have been infected with venereal disease may contribute to the present higher death rate. Such complications were not common in the country when I was practicing.

One case, which I had, was rather unusual: a Dutch woman, only recently over from Holland, gave birth to a baby on a Saturday night. I saw that there was another one coming and waited quite a while, but finally decided to go home and wait until I was called. A week from the following Monday, the patient did a large washing and that night I assisted her with the birth of the second baby. She made a good recovery. Another patient, a primipara, attended a neighborhood party the day after her baby was born and took part in the dancing. If the experience hurt her in any way, there was no evidence of it.

I have left the most unusual case I ever saw for the last. I was called by a man who said that his wife had given birth to a baby some hours before, and that the two old ladies who had cared for her had advised him to obtain the services of a physician as quickly as possible because she looked terribly ill. I went with him immediately and when we came to the home I could see that she had been bled white. There was no pulse at the wrist and only very feeble heart sounds were audible with the stethoscope. It was evident that she was about to die, so I told him that she was beyond the benefit of any treatment and that, if he and his wife had anything to say to each other, it should be done quickly. Instead of complying, he ran out and told his boys to get on horseback and to bring back as many physicians as they could find. When he returned to the house, his wife was dead. The two old ladies told me that they had repeatedly suggested to the patient that she have a doctor, but that she had insisted that the pains were not yet sufficiently strong. Finally, she had one terrific pain, the most agonizing they had ever seen, during which the head was born. There were no more pains, but the two old ladies extracted the rest of the child by drawing the head down until the body was delivered, and then cut the cord. The two ladies went to another room to wash and dress the baby, and then went back to see how the mother was getting on. They found her looking terribly bad and immediately had the husband come for me. The child, which was the patient's twelfth or thirteenth, weighed 21 pounds and is still living. She was not more than average in size and was the mother of quite a bunch of children. What happened, of course, was a rupture of the uterus with hemorrhage into the abdominal cavity. I think that this was a case of carrying a child much past the normal time.

Now, Dr. Plass, this is probably not exactly what you want, but on the other hand it is. These people had as good care, perhaps better, than most mothers have now, because the physiologic processes were allowed to go on without interference, and it is after all the duty of the physician to allow nature every opportunity to do its own work in its own way. It is wonderful how an overly large head and a small birth canal, if given plenty of time, will conform to each other with a resulting normal delivery.

Remember, too, that in all these confinements I had consultation only four times, the balance were taken care of by myself with such assistance as was available in the home or in the immediate neighborhood. Doctors were few and far apart and, since each had his own work to do, we became accustomed to taking the entire responsibility upon ourselves. The roads were atrocious, only dirt roads, and sometimes next to impassable. I did most of my traveling on horseback with a saddle bag for medicines and instruments. I would start out in the morning, make a round trip, and frequently on getting home would find other work waiting for me. If I were a young man again, I would set myself up as a specialist in obstetrics, although I fear that the modern mother would not approve of my ways. I believe that many obstetric difficulties would disappear if our women would develop their muscles from childhood up by suitable housework—doing the family laundry, scrubbing, and other heavier tasks.

I am too old to take up the practice of medicine any more: it is now nearly 52 years since I left Iowa City and engaged in practice. I was a general practi-

tioner—17 specialists rolled into one, as I heard the general man described by one of our number in answer to an attorney's question concerning the difference between him and a specialist.

Fraternally and sincerely yours,

FERDINAND J. SMITH, M.D.

The writer of this letter, Dr. Ferdinand J. Smith, was born in Chicago, February 27, 1862. In 1883, he received the B.S. degree from the Iowa State College (Ames), and the following year, 1883-84, was Instructor at the Massachusetts Institute of Technology. During 1884, he also spent some time in Germany and was made a member of the Deutsche Medizinische Gesellschaft in Berlin. From 1884 to 1887 he attended the College of Medicine, State University of Iowa, and was graduated in March, 1887, with the M.D. degree.

Immediately after graduation, he settled in Alton, Iowa, where he did general practice until 1904, when he went to Des Moines as Dean of the Junior College of Medicine and Head of the Department of Biological Chemistry at Drake University, after having spent some months at Heidelberg in Kossel's laboratory. In 1909, he was made Dean of Men at the University, a position which he held until 1913, when the Drake Medical Department was discontinued. During his early years as a practitioner, Dr. Smith was surgeon to the C. & N. W. R. R. (1887) and to the C. M. St. P. and Omaha R. R. (1889).

Upon leaving Des Moines in 1913, he resumed the practice of medicine at Little Rock, Iowa, where he remained until his retirement. During this interval he was active in medical society work and helped to organize the Northwest Iowa Medical Association. From 1918 to 1919 he served as coroner for Lyon County and at one time was Bacteriologist to the Auxiliary State Health Laboratory for Northwest Iowa. As late as 1937, he was President of the Dickinson County Interprofessional Association. In spite of a heavy professional burden, Dr. Smith prepared many papers on medical subjects. Within the last few years he published "The Transition from Franklin Medical School to the Keokuk College of Medicine of the State University of Iowa," an interesting treatise dealing with the early history of medical education in the state.

To the Editor:

In the paper by Herrell on "Studies on the Endometrium in Association with the Normal Menstrual Cycle, with Ovarian Dysfunctions and Cancer of the Uterus," published in the April number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, the author takes issue with a number of authors, including Novak and Yui, that hyperplasia of the endometrium is often found in association with adenocarcinoma of the uterus, and then presents very impressive evidence from his own series of cases that such an association is exceedingly common. He prefers, however, to apply to the Swiss-cheese pattern of proliferative endometrium the designation of "proliferative type of endometrium with cystic change." He does not, in quoting our paper, explain that we particularly emphasized that only the postmenopausal type of hyperplasia was considered important from this standpoint, and that we took great pains to discuss the frequent misapplication of the term hyperplasia, which, however, is so firmly entrenched in the literature that no one individual's fiat will dislodge it.

"The term hyperplasia, therefore, as we have many times stressed, is a rather loose and not an altogether satisfactory one; but it is now so well established that it would not be easy to dislodge it. The proper evaluation of the histologic variations of hyperplasia can be made only if one bears in mind that they represent merely the reaction of the endometrium to varying degrees of estrin stimulation, and that there is an insensible gradation from the normal proliferative or interval type of endometrium to the so-called mild hyperplasia than to the hyperplasia of frank

'Swiss-cheese' pattern, and finally to the markedly proliferative hyperplasia pictures which may even closely resemble cancer.'' (This is an exact quotation from our paper.)

If one considers the causation of hyperplasia, it is not at all paradoxical, strange though it seems to be to Dr. Herrell, that it may be associated with amenorrhea, menorrhagia or sterility, though no one now ''blames'' the endometrial lesion for any of these symptoms of the underlying endocrinopathy.

No one can take exception to his description of the menstrual phases, which is essentially what has been accepted for the past quarter of a century or more, though Dr. Herrell seems to like the term ''differentiative'' rather than the more generally used terms ''luteal'' or ''secretory.'' It is gratifying to us, too, to note that he has fully confirmed our own findings that proliferative endometrial activity is not uncommon in postmenopausal women, and that such postmenstrual endometrial proliferative pictures are frequently associated with adenocarcinoma. This was the whole point of our paper, and Dr. Herrell seems to have missed it quite completely. This is not the place to discuss a number of other points in Dr. Herrell's paper, such as the interpretation of some of the microscopic findings (I feel sure, for example, that most gynecological pathologists would consider the picture in Fig. 11 perfectly benign and not typical adenocarcinoma Grade I), but I did want to get the record straight as to what we tried to show in our own paper, as this would not be apparent from Dr. Herrell's reference to it.

EMIL NOVAK, M.D.

26 East Preston Street
Baltimore, Md.
April 13, 1939.

To the Editor:

If my answer to Dr. Novak's letter is brief, my intention is not to be curt. However, I believe my answer is contained in the paper to which Dr. Novak objects.

In the first two paragraphs on page 564 of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, April, 1939, I pointed out certain discrepancies in definition and in reported facts which have appeared in the literature. I believe, and so did my associates who knew my work, that I had explained these discrepancies and pointed out a way to avoid them. My work was carefully planned and executed; the pathology has been checked repeatedly by outstanding pathologists and the conclusions verified. My purpose was to clarify and to contribute at least some new knowledge, not to tear down or contradict.

WALLACE E. HERRELL, M.D.

The Mayo Clinic
Rochester, Minnesota
April 18, 1939

Books Received

A TEXTBOOK OF NEURO-RADIOLOGY. By Cecil P. G. Wakely, Fellow of King's College, London; Senior Surgeon, King's College Hospital, London, etc., and Alexander Orley, Fellow of British Association of Radiologists; Radiologist of West End Hospital for Nervous Diseases, etc. Illustrated, 336 pages. Williams & Wilkins Co., Baltimore, 1939.

PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY. Volume II. By H. B. Van Dyke, Head of Division of Pharmacology, Squibb's Institute for Medical Research, etc. Illustrated, 402 pages. University of Chicago Press, Chicago, 1939.

PHYSIOLOGY OF THE UTERUS. With Clinical Correlations. By Samuel R. M. Reynolds, Fellow, John Simon Guggenheim Memorial Foundation, University of Rochester School of Medicine and Dentistry, Associate Professor of Physiology, Long Island College of Medicine, Brooklyn, N. Y. Illustrated, 447 pages. Paul B. Hoeber, Inc., New York, 1939.

THE VAGINAL DIAPHRAGM. By Dr. Le Mon Clark, Chicago. Illustrated, 107 pages. The C. V. Mosby Co., St. Louis, 1939.

LEHRBUCH DER FRAUENHEILKUNDE, in zwei Baenden. Von Professor Dr. W. Weibel, Vorstand der II. Universitaets-Frauenklinik in Wien. Zweiter Band: Gynaekologie. Mit 531 zum Teile mehrfarbigen Abbildungen im Text mit 16 farbigen Tafeln, 398 Seiten. Urban & Schwarzenberg, Berlin-Wien, 1939.

L'OBSTÉTRIQUE A TRAVERS LES AGES. Par L. Devraigne, Accoucheur de Lariboisière, etc. Avec 77 figures dans le texte, 138 pages. Gaston Doin & Cie, Paris, 1939.

PROBLEMS OF AGEING. Biological and Medical Aspects. Edited by E. V. Cowdry, Washington University in St. Louis. 121 illustrations, 758 pages. Williams & Wilkins Company, Baltimore, 1939.

FEMININE HYGIENE IN MARRIAGE. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 155 pages. Harvest House, New York, 1938.

SUPERFLUOUS HAIR AND ITS REMOVAL. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 155 pages. Harvest House, New York, 1938.

LEHRBUCH DER GEBURTSHILFE. Herausgegeben von Professor Dr. W. Stoeckel, Universitaets-Frauenklinik in Berlin. Fuenfte, verbesserte Auflage, mit 639 zum grossen Teile farbigen Abbildungen im Text, 1054 Seiten. Verlag von Gustav Fischer, Jena, 1938.

Items

American Congress On Obstetrics and Gynecology

The attention of the readers of the JOURNAL is called to the American Congress on Obstetrics and Gynecology, which is scheduled to meet in Cleveland, Ohio, on September 11-15, 1939.

Applications for membership should be addressed to the Headquarters, 650 Rush Street, Chicago, Ill.

Pacific Coast Society of Obstetrics and Gynecology

The next meeting of the Pacific Coast Society of Obstetrics and Gynecology will be held in Portland, Oregon, October 4 to 7, 1939. For further information apply to T. Floyd Bell, Secretary-Treasurer, 400 Twenty-Ninth St., Oakland, Calif.

Third All India Obstetric and Gynaecological Congress

The Third All India Obstetric and Gynaecological Congress will be held in Calcutta in December, 1939. The principal subjects of discussion will be: Anemia of pregnancy, functional uterine hemorrhage, and maternity and child welfare. The Provisional Scientific Committee has formulated a scheme to facilitate investigations on those subjects. The Secretary will be at the service of any investigator to supply any relevant information. All communications are to be addressed to Dr. S. Mitra, Secretary, Provisional Scientific Committee, 3, Chowringhee Terrace, Calcutta.

Poliomyelitis Associated with Pregnancy

Under a grant from the National Foundation for Infantile Paralysis, an investigation is being conducted at the Hospital for Joint Diseases in New York City of the obstetric difficulties in patients who have had infantile paralysis. The assistance of physicians who have encountered such cases is asked by those in charge of this research, Dr. Samuel Kleinberg and Dr. M. T. Horwitz, who may be addressed for questionnaire blanks and further information, at the Hospital for Joint Diseases, Madison Avenue and 123rd Street, New York City.

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